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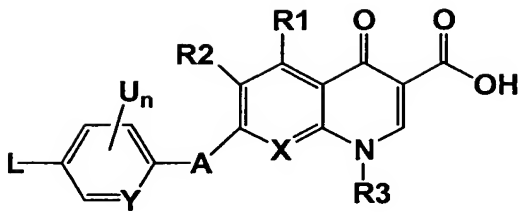
Use of oxazolidinone-quinoline hybrid antibiotics for the treatment of anthrax and other infections

The present invention describes the use of compounds in which the pharmacophores of quinolone and oxazolidinone are chemically linked together through a linker that is stable under physiological conditions for the treatment of anthrax and other infections.

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax most commonly occurs in wild and domestic lower vertebrates (cattle, sheep, goats, camels, antelopes, and other herbivores), but it can also occur in humans when they are exposed to infected animals or tissue from infected animals. *Bacillus anthracis*, the etiologic agent of anthrax, is a large, gram-positive, non-motile, spore-forming bacterial rod. The three virulence factors of *B. anthracis* are edema toxin, lethal toxin and a capsular antigen. Human anthrax has three major clinical forms: cutaneous, inhalation, and gastrointestinal. If left untreated, anthrax in all forms can lead to septicemia and death. Recently, anthrax has become of considerable interest, because it is considered to be a potential agent for use in biological warfare.

The present invention provides the use of compounds of Formula (I) for the treatment of anthrax and other infections:

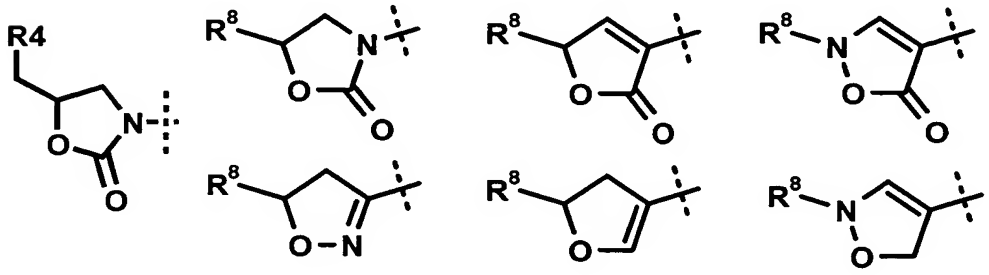


(I)

wherein

A is a direct bond, a NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, -CO-O-, -NH-CO-O-, -O-Z-heterocycloalkylen, an alkylen group, an alkenylen group, an alkinylen group, a heteroalkylen group, an arylen group, a heteroarylen group, a cycloalkylen group, a heterocycloalkylen group, an alkylarylen group or a heteroarylalkylen group or a combination of two or more of these atoms or groups;

L is selected from the following groups:



X is CR5 or N;

Y is CR6 or N;

U is F or Cl;

Z is a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group or a C_{1-4} heteroalkylene group, all of which may be substituted by one or more hydroxy or amino groups;

n is 0, 1, 2 or 3;

R1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

R2 is H, F or Cl;

R3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group; all of which may be substituted with one, two or more halogen atoms like F or Cl;

R4 is a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group;

R5 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R3 and R5 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a

cycloalkylen or heterocyclo-alkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl;

R6 is H, F, Cl or OMe;

R8 is a C_{1-6} heteroalkyl or a heteroarylalkyl group;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof.

It should be appreciated that certain compounds of Formula (I), or Formula (II) or (III) of the present application, may have tautomeric forms from which only one might be specifically mentioned or depicted in the following description, different geometrical isomers (which are usually denoted as cis/trans isomers or more generally as (E) and (Z) isomers) or different optical isomers as a result of one or more chiral carbon atoms (which are usually nomenclatured under the Cahn-Ingold-Prelog or R/S system). Further, some compounds may display polymorphism. All these tautomeric forms, geometrical or optical isomers (as well as racemates and diastereomers) and polymorphous forms are included in the invention.

The term alkyl refers to a saturated or unsaturated (i.e. alkenyl and alkinyl) straight or branched chain alkyl group, containing from one to ten, preferably one to six carbon atoms for example methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl n-hexyl, 2,2-dimethylbutyl, n-octyl; ethenyl (vinyl), propenyl (allyl), iso-propenyl, n-pentyl, butenyl, isoprenyl or hexa-2-enyl; ethinyl,

propinyl or butinyl groups. Any alkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The terms alkenyl and alkinyl refer to an unsaturated straight or branched chain alkyl group (having one, two or more double and/or triple bonds, an alkenyl preferably having one or two double bonds and an alkinyl preferably having one or two triple bonds), containing from two to ten, preferably two to six carbon atoms for example: ethenyl (vinyl), propenyl (allyl), iso-propenyl, n-pentenyl, butenyl, isoprenyl or hexa-2-enyl; ethinyl, propinyl or butinyl groups. Any alkenyl or alkinyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term heteroalkyl refers to an alkyl group as defined herein where one or more carbon atoms are replaced by an oxygen, nitrogen, phosphorous or sulphur atom for example an alkoxy group such as methoxy, ethoxy, propoxy, iso-propoxy, butoxy or tert.-butoxy, an alkoxyalkyl group such as methoxymethyl, ethoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, an alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino or diethylamino, an alkylthio group such as methylthio, ethylthio or isopropylthio or a cyano group. It may also refer to one of the above groups containing a keto group. The term heteroalkyl furthermore refers to a group derived from a carboxylic acid or carboxylic acid amide such as acetyl, propionyl, acetyloxy, propionyloxy,

acetylamino or propionylamino, a carboxyalkyl group such as carboxymethyl, carboxyethyl or carboxypropyl, a carboxyalkyl ester, an alkylthiocarboxyamino group, an alkoxyimino group, an alkylaminothiocarboxyamino group or an alkoxycarbonylamino group. Any heteroalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term cycloalkyl refers to a saturated or partially unsaturated (having one, two or more double and/or triple bonds), cyclic group with one, two or more rings, having three to 14 carbon ring-atoms, preferably from five or six to ten carbon ring-atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetralin, cyclopentenyl or cyclohex-2-enyl groups. Any cycloalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino, cyanide, or a group of the formula -OR7, wherein R7 is hydrogen, a group of formula $PO_3R^9{}_2$ or SO_3R^{10} or a heteroalkyl group carrying at least one OH, NH_2, SO_3R^{10}, $PO_3R^9{}_2$ or COOH group, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl.

The term heterocycloalkyl refers to a cycloalkyl group as defined herein where one, two or more carbon ring-atoms are replaced by one, two or more oxygen, nitrogen, phosphorous or sulphur atoms or $S(0)_{1-2}$ groups for example piperidino, morpholino or piperazino groups, preferably such groups contain 1 or 2 nitrogen atoms.

The term aryl refers to an aromatic cyclic group with one, two or more rings, having five to 14 carbon ring-atoms preferably from five or six to ten carbon ring-atoms, for example phenyl or naphthyl groups. Any aryl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino or cyanide.

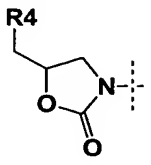
The term heteroaryl refers to an aryl group as defined herein where one, two or more ring-carbon atoms are replaced by an oxygen, nitrogen, boron, phosphorous or sulphur atom, for example pyridyl, imidazolyl, pyrazolyl, quinolinyl, isoquinolinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl and pyridazinyl groups.

The terms arylalkyl, alkylaryl and heteroarylalkyl, heteroalkylaryl refer to groups that comprise both aryl or, respectively, heteroaryl as well as alkyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups.

Preferred embodiments of the present invention are compounds of Formula (I), wherein

A is a bond, a NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, -CO-O-, -NH-CO-O-, an alkylen group, an alkenylen group, an alkinylen group, a

heteroalkylen group, an arylen group, a heteroarylen group, a cycloalkylen group, a heterocycloalkylen group, an alkylarylen group or a heteroarylalkylen group or a combination of two or more of these atoms or groups;

L is 

;

X is CR5 or N;

Y is CR6 or N;

U is F or Cl;

n is 0, 1, 2 or 3;

R1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

R2 is H, F or Cl;

R3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group;

R4 is a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl

group, an alkylaryl group or a heteroarylalkyl group;

R5 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R3 and R5 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a cycloalkylen or heterocyclo-alkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl;

R6 is H, F, Cl or OMe;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof for the treatment of anthrax.

Preferred and/or advantageous embodiments of the invention are subject-matter of the subclaims.

Preferred are compounds of Formula (I), wherein R1 is H or NH_2 (especially H).

Further preferred are compounds of Formula (I), wherein R2 is H or F (especially F).

Moreover preferred are compounds of Formula (I), wherein R3 is an ethyl, a 2-propyl, a C3-C6 cycloalkyl, a phenyl or a pyridyl group. All these groups may be substituted by one, two or more fluorine atoms or amino groups.

Moreover preferred are compounds of Formula (I), wherein R3 is a cyclopropyl group.

Further preferred are compounds of Formula (I), wherein R3 and R5 together form a bridge of the formula -O-CH_2-N(Me)- or -O-CH_2-CH(Me)-. Herein, the preferred stereochemistry at the chiral center is the one giving the (S) configuration in the final compound.

Further preferred are compounds of Formula (I), wherein R4 is a group of the formula -NHCOCH=CHAryl, -OHeteroaryl (especially -oxa-3-oxazol), -$NHSO_2$Me, -NHCOOMe, $NHCS_2$Me, $NHCSNH_2$, -NHCSOMe or -NHCOMe.

Especially preferred are compounds of Formula (I), wherein R4 is an acetylamino group.

Further preferred are compounds of Formula (I), wherein the absolute configuration at C-5 of the oxazolidinone ring is (S) according to the Cahn-Ingold-Prelog nomenclature system.

Moreover preferred are compounds of Formula (I), wherein R5 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms or a CF_3 group.

Further preferred are compounds of Formula (I), wherein X is N or CH.

Further preferred are compounds of Formula (I), wherein Y is N or CF (especially CF).

Further preferred are compounds of Formula (I), wherein n is 0.

Further preferred are compounds of Formula (I), wherein A is a bond.

Further preferred are compounds of Formular (I), wherein A is a group of the formula

$$-B_{0-1}-\left[D-E_{0-1}\right]_m-G_{0-1}-K_{0-1}-$$

wherein

the group B is NH, O, S, SO, SO_2, SO_2NH, an alkylene, which may be substituted by one, two or more fluorine atoms or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group;

the groups D independently of each other are optionally anellated heterocycloalkylen groups with 1, 2, 3 or 4 nitrogen atoms, which heterocycloalkylen groups may each be substituted by one, two or more fluorine atoms and/or which each may be substituted at one, two, three or four nitrogen atoms by an alkyl or an acyl group;

the groups E independently of each other are NH, O, S, SO, SO_2, SO_2NH, an alkylene, which may be substituted by one, two or more fluorine atoms or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group;

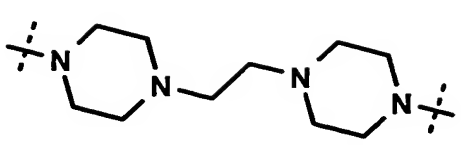
the groups G independently of each other are optionally anellated heterocycloalkylen groups with 1, 2,

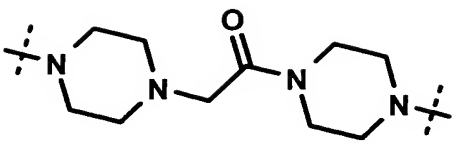
3 or 4 nitrogen atoms, which heterocycloalkylen groups may each be substituted by one, two or more fluorine atoms and/or which each may be substituted at one, two, three or four nitrogen atoms by an alkyl or an acyl group;

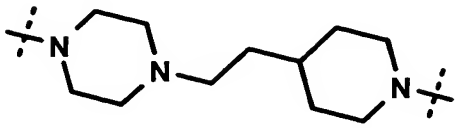
the group K is NH, O, S, SO, SO_2, SO_2NH, an alkylene, which may be substituted by one, two or more fluorine atoms or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group; and m = 1,2,3 or 4.

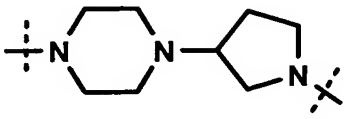
Moreover preferred are compounds of Formula (I), wherein A is a cycloalkylen or a alkylcycloalkylen group that contains 2, 3 or 4 heteroatoms (preferred O, N and S) and may be substituted by one, two or more fluorine atoms and the nitrogen atoms may be substituted by an alkyl or an acyl group.

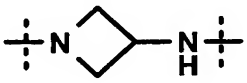
Further preferred are compounds of Formula (I), wherein A is selected from the following groups which may be further substituted by one, two or more fluorine atoms or by an alkyl group which may be substituted by one, two or more fluorine atoms, and wherein the amino groups may be substituted by an alkyl or an acyl group:

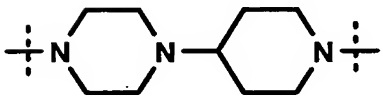












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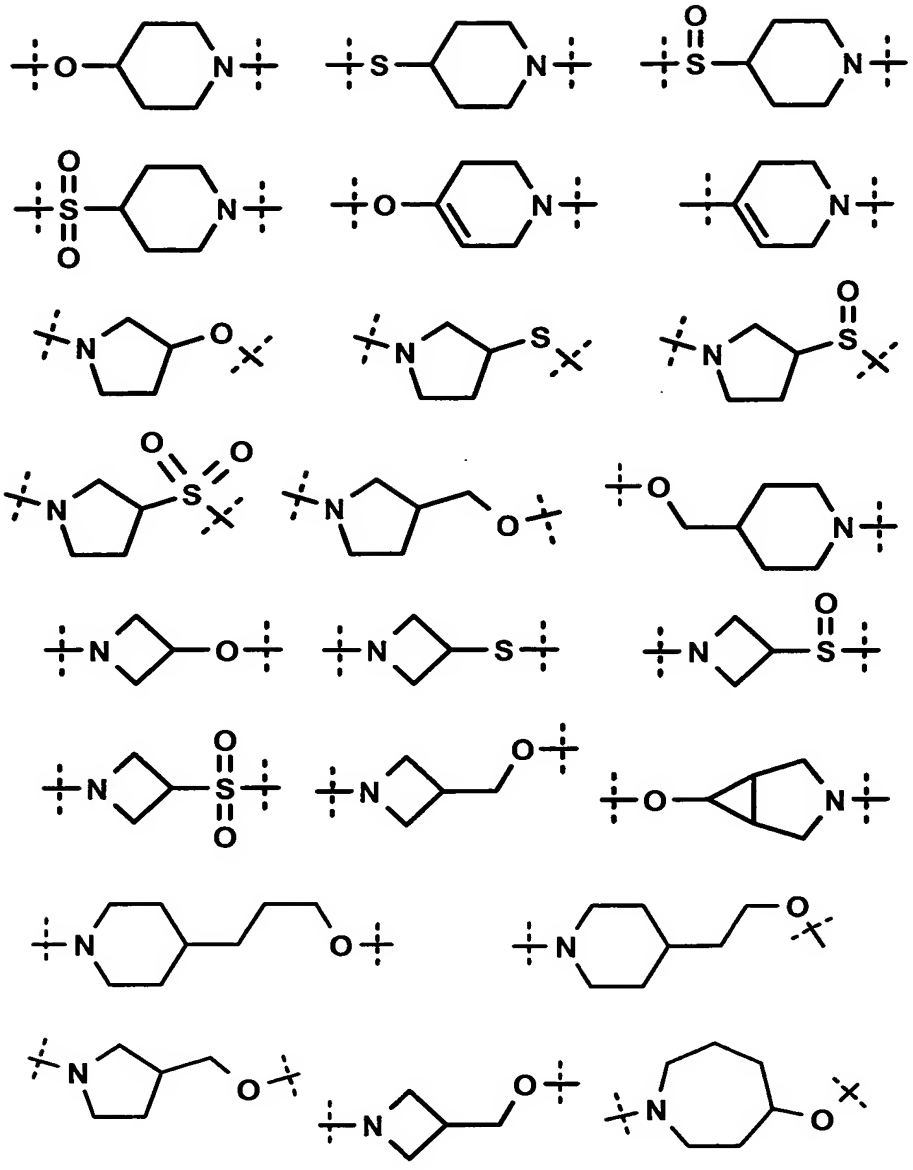
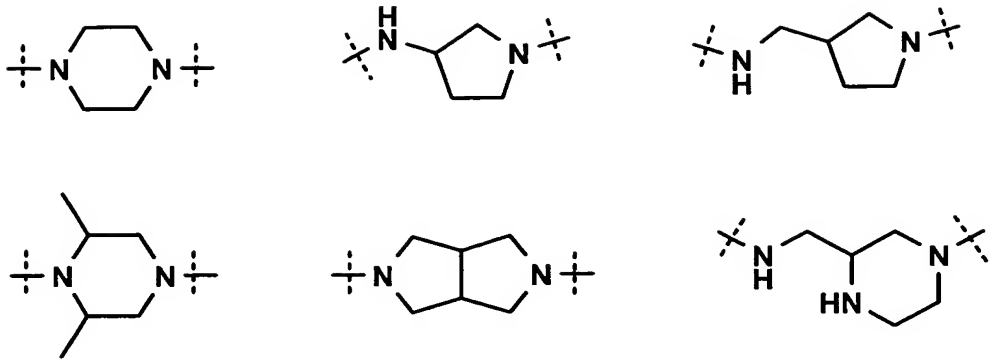
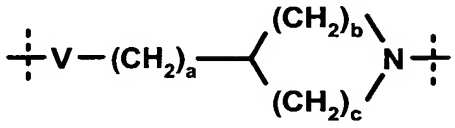




Moreover preferred are compounds of Formula (I), wherein A is a group of the formula -V-W-, wherein V is a direct bond or a group of the formula NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, $-CH_2-$, -CO-O-, $-(CH_2)_{1-3}-O-$, -CH=CH-C(O)-, or -NH-CO-O- and W is a heterocycloalkyl group with 4 to 7 ring atoms or a alkylheterocycloalkyl group with 4 to 7 ring atoms and 1 to 4 carbon atoms in the alkyl chain; all these groups may be substituted by 1, 2, 3 or 4 fluorine atoms, methyl or methoxy groups.

Further preferred are compounds of Formula (I), wherein A is a group of the formula



wherein V is a group of the formula NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, $-CH_2-$, -CO-O-, $-(CH_2)_{1-3}-O-$, -CH=CH-C(O)-, or -NH-CO-O-; a is 0, 1, 2, 3 or 4; b is 0, 1, 2, 3 or 4; c is 0, 1, 2, 3 or 4 and 1, 2, 3

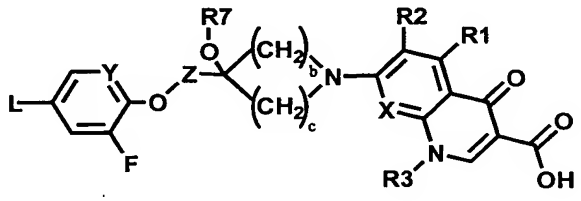
or 4 hydrogen atoms may be substituted by F, a methyl- or a methoxy group.

Moreover preferred are compounds as described here, wherein V is NH, O, S, SO or SO_2.

Especially preferred are compounds as described here, wherein V is O or NH; a is 0 or 1; b is 1 or 2 and c is 1 or 2.

Moreover preferred are compounds as described here, wherein A is a group of the formula OCH_2Het, wherein Het is an optionally substituted heterocycloalkylen group with 4, 5, 6 or 7 ring atoms.

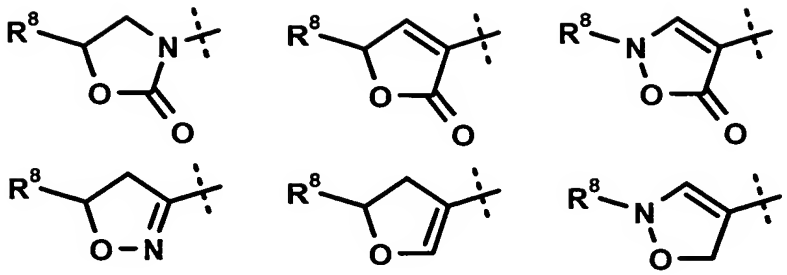
Another preferred embodiment of the present invention are compounds of Formula (II):



(II)

wherein

L is selected from following groups:



X is CR5 or N;

Y is CR6 or N;

Z is a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group or a C_{1-4} heteroalkylene group, all of which may be substituted by one or more hydroxy or amino groups;

b is 1, 2 or 3;

c is 1, 2 or 3;

R1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

R2 is H, F or Cl;

R3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group; all of which may be substituted with one, two or more halogen atoms like F or Cl.

R5 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R3 and R5 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a cycloalkylen or heterocyclo-alkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl;

R6 is H, F, Cl or OMe;

R7 is hydrogen, a group of formula $PO_3R^9{}_2$ or SO_3R^{10} or a heteroalkyl group carrying at least one OH, NH_2, SO_3R^{10}, $PO_3R^9{}_2$ or COOH group, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl,

R8 is a C_{1-6} heteroalkyl or a heteroarylalkyl group;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof.

Further preferred are compounds of Formula (II), wherein R1 is H.

Further preferred are compounds of Formula (II), wherein R2 is F or H.

Moreover preferred are compounds of Formula (II), wherein R3 is an ethyl, a 2-propyl, a C3-C6 cycloalkyl, a phenyl or a pyridyl group. All these groups may be substituted by one, two or more fluorine atoms or amino groups.

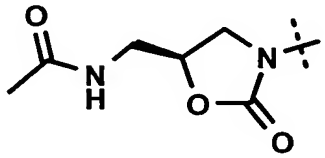
Moreover preferred are compounds of Formula (II), wherein R3 is a cyclopropyl group.

Further preferred are compounds of Formula (II), wherein R3 and R5 together form a bridge of the formula -O-CH_2-N(Me)- or -O-CH_2-CH(Me)-. Herein, the preferred stereochemistry at the chiral center is the one giving the S configuration in the final compound.

Moreover preferred are compounds of Formula (II), wherein R7 is hydrogen or a group of formula PO_3H_2 , SO_3R^{10}, $PO_3R^9{}_2$, $CH_2OPO_3H_2$ or $COCH_2CH_2COOH$, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl or together with the oxygen to which it is bound forms an ester of a naturally occurring amino acid or a derivative thereof (e.g dimethyl aminoglycine).

Further preferred are compounds of Formula (II), wherein R^8 is a group of the formula -CH_2NHCOCH=CHAryl, -CH_2OHeteroaryl (especially -oxa-3-oxazol), -CH_2NHSO_2Me, -$CH_2NHCOOMe$, -CH_2NHCS_2Me, -$CH_2NHCSNH_2$, -$CH_2NHCSOMe$ or -$CH_2NHCOMe$.

Especially preferred are compounds of Formula (II), wherein L has the following structure:



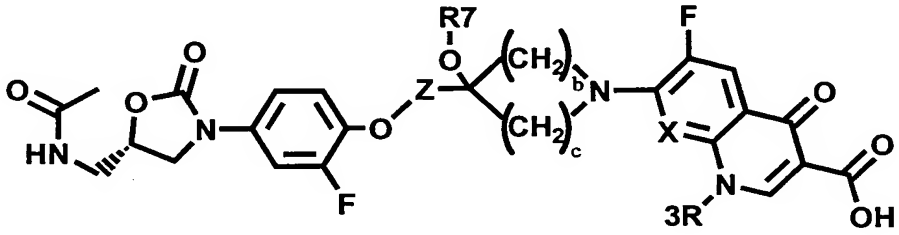
Moreover preferred are compounds of Formula (II), wherein R5 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms.

Further preferred are compounds of Formula (II), wherein X is N or CH.

Moreover preferred are compounds of Formula (II), wherein Y is CH.

Further preferred are compounds of Formula (II), wherein Z is CH_2 or CH_2CH_2.

Especially preferred are compounds of Formula (III)



(III)

wherein Z is CH_2 or CH_2CH_2; X is CH, N or C-OMe and R3 is cyclopropyl or X is CR5 and R5 and R3 together form a bridge of the formula -O-CH_2-CH(Me)-, wherein, the preferred stereochemistry at the chiral center is the one giving the S configuration in the final compound and b, c and R7 are the same as defined above.

The present invention also relates to pharmacologically acceptable salts, or solvates and hydrates, respectively, and to compositions and formulations of compounds of Formula (I), (II), or (III). The present

invention describes procedures to produce pharmaceutically useful agents, which contain these compounds, as well as the use of these compounds for the production of pharmaceutically useful agents.

The pharmaceutical compositions according to the present invention contain at least one compound of Formula (I), (II) or (III) as the active agent and optionally carriers and/or diluents and/or adjuvants. Optionally the pharmaceutical compositions according to the present invention may also contain additional known antibiotics.

Examples of pharmacologically acceptable salts of sufficiently basic compounds of Formula (I) and of compounds of Formula (II) or (III) are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound of Formula (I) may form alkali or earth alkaline metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts; all of which are also further examples of salts of Formula (II) or (III). Compounds of Formula (I), (II) or (III) may be solvated, especially hydrated. The hydratisation can occur during the process of production or as a

consequence of the hygroscopic nature of the initially water free compounds of Formula (I), (II) or (III). The compounds of Formula (I), (II) or (III) contain asymmetric C-atoms and may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds.

The present invention also relates to pro-drugs which are composed of a compound of Formula (I), (II) or (III) and at least one pharmacologically acceptable protective group which will be cleaved off under physiological conditions, such as an alkoxy-, aralkyloxy-, acyl-, acyloxymethyl group (e.g. pivaloyloxymethyl), an 2-alkyl-, 2-aryl- or 2-aralkyl-oxycarbonyl-2-alkylidene ethyl group or an acyloxy group as defined herein, e.g. ethoxy, benzyloxy, acetyl or acetyloxy or, especially for a compound of Formula (I), for hydroxy group (ROH), a sulfate, a phosphate ($ROPO_3$ or $ROCH_2OPO_3$) or an ester of an amino acid. Especially preferred are pro-drugs of the hydroxy group of a compound of Formula (II) or (III) wherein R7 is H.

As mentioned above, therapeutically useful agents that contain compounds of Formula (I), (II) or (III), their solvates, salts or formulations are also comprised in the scope of the present invention. In general, compounds of Formula (I), (II) or (III) will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or hard capsules, for example

soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containg the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatin, malt, silica gel, starch or derivatives thereof, talc, stearinic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use as excipients e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, lipids, phospholipids, cyclodextrins, vegetable, petroleum, animal or synthetic oils. Especially preferred are lipids and more preferred are phospholipids (preferred of natural origin; especially preferred with a particle size between 300 to 350 nm) preferred in phosphate buffered saline (pH = 7 to 8, preferred 7.4). For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents

may also contain additives for conservation, stabilisation, e.g. UV stabilizers, emulsifiers, sweetener, aromatisers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

A daily dosage per patient of about 1 mg to about 4000 mg especially about 50 mg to 3 g is usual with those of ordinary skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals, and the kind of diseases being treated or prevented. The daily dosage can be administrated in a single dose or can be divided over several doses. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg and 2000 mg can be contemplated.

The invention also relates to a method of treating a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises administering to the mammal, fish or bird a combination comprising a compound of Formula (I), (II) or (III) and another antibiotic, wherein the amounts of the compound and of the other antibiotic are together therapeutically effective in treating the disorder. In further embodiments, the compound of the invention may administered prior to, with or after the other antibiotic. Examples of suitable other antibiotics include, but are not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating,

inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

As used herein, unless otherwise indicated, the terms or phrases "infection(s)", "bacterial infection(s)", "protozoal infection(s)", and "disorders related to bacterial infections or protozoal infections" include the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by Streptococcus pneumoniae, Haemophilus *influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. faecium*, *E. casselflavus*, *S. epidermidis*, *S. haemolyticus*, or *Peptosfreptococcus* spp.; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Corynebacferium diphtheriae*, or *Acfinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; blood and tissue infections, including endocarditis and osteomyelitis, caused by *S. aureus*, *S. haemolyficus*, *E. faecalis*, *E. faecium*, *E. durans*, including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides; uncomplicated skin and soft tissue infections and abscesses, and puerperal fever related to infection by *Staphylococcus aureus*, coagulase-negative staphylococci (i.e., *S. epidermidis*, *S.*

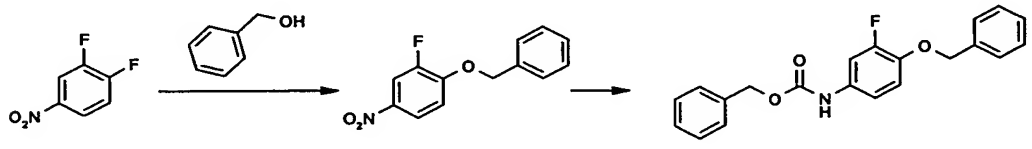
hemolyticus, etc.), *Streptococcus pyogenes*, *Streptococcus agalactiae,* Streptococcal groups C-F (minute colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Closfridium* spp., or *Bartonella henselae;* uncomplicated acute urinary tract infections related to infection by *Staphylococcus aureus,* coagulase-negative staphylococcal species, or *Enterococcus* spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidurn, Ureaplasma urealyticum,* or *Neiserria gonorrheae;* toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori;* systemic febrile syndromes related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* infections caused by *Mycobacferium tuberculosis, M. leprae, M. paratuberculosis, M. kansasii,* or *M. chelonei;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Closfridium perfringens* or *Bacteroides* spp.; and atherosclerosis or

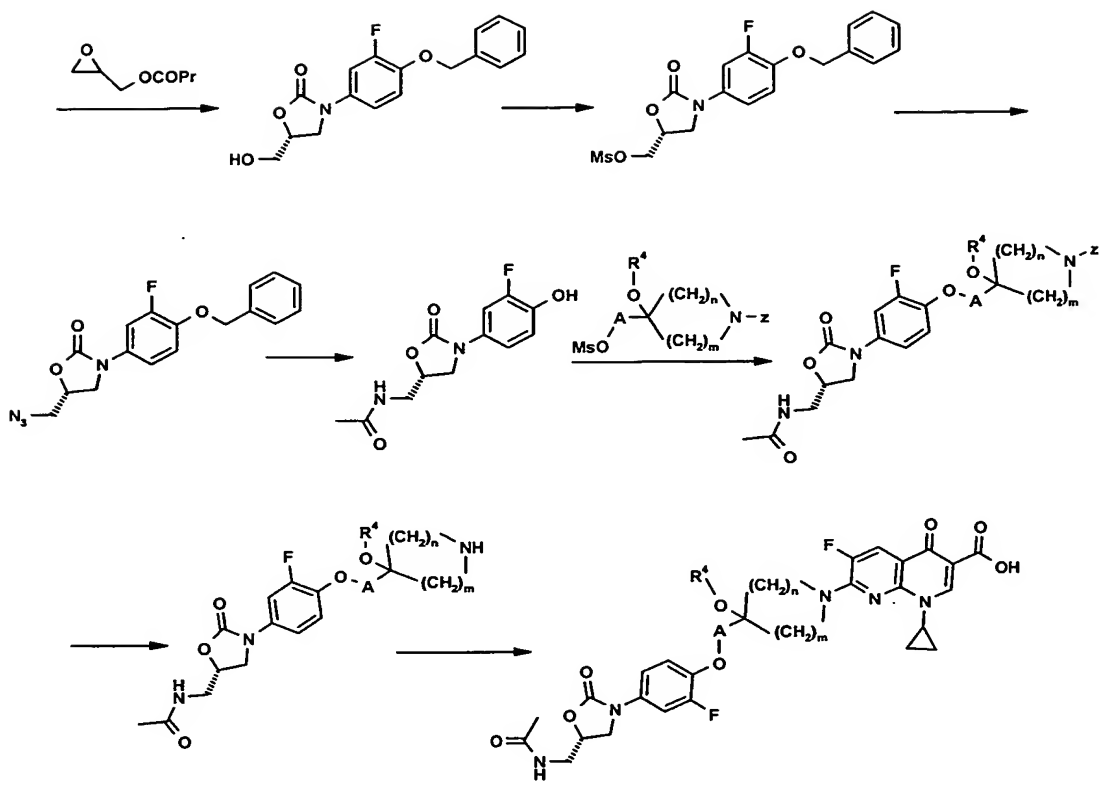
cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*.

Preferred is the use of a compound according to Formula (I), (II) or (III) for the treatment of infections that are mediated by Gram-negative bacteria such as E. coli, Klebsiella pneumoniae and other enterobacteriaceae, Haemophilus influenzae, Moraxella catarrhalis, Acinetobacter spp., Stenothrophomonas maltophilia, Neisseria gonorrhoeae, Neisseria menigitidis, Helicobacter pylori, Campylobacter spp., Mycoplasma spp. and Legionella pneumophilia or Gram-positives such as Bacillus cereus, Bacillus anthracis, Strep. pneumoniae, Corynebacterium spp., Propionibacterium acnes and Listeria monocytogenes.

In the following the invention is described in more detail with reference to examples. These examples are intended for illustration only and are not to be construed as any limitation. The Examples were synthesized according to the procedures described in WO03032962, WO03031443, US 60/530,822 and C. Hubschwerlen et al. Bioorg. Med. Chem. 2003, 11, 2313-2319.

The compounds of Formula (II) and (III) can be synthesized according to the following reaction scheme:



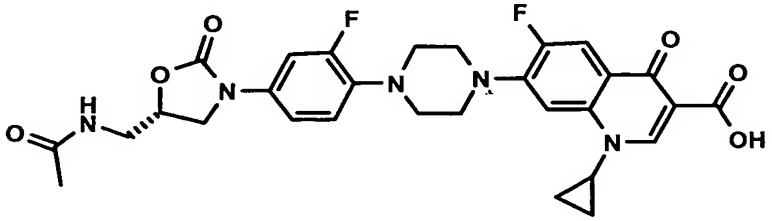


Reaction conditions:

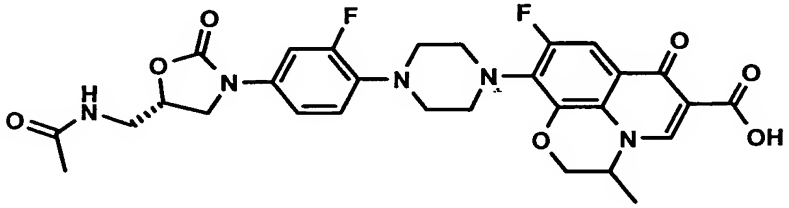
Step 1: CH_2Cl_2, KOH (50%), 3h, rt; 97%. step 2: H_2, Pt/C, 20h, rt; followed by Z-Cl, acetone/water, $NaHCO_3$, 12h, rt, 98%. step 3: n-BuLi, -60°C, 24h, 80%. step 4: MsCl, triethylamine, CH_2Cl_2; 100%. step 5: NaN_3 in DMF, 90°C, cat. Bu_4NI, 5h, 90%. step 6: H_2, $Pd(OH)_2$, THF, MeOH, 24h, followed by AcOH, Ac_2O, rt, 2h, 70%. step 7: DMF, NaH, 70°C, 12h, 75%. step 8: H_2, $Pd(OH)_2$, MeOH, THF, 24h, RT, 100%. step 9: N-Methylpyrrolidinone, 1-Cyclopropyl-7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthydrin-3-carboxylic acid (commercially available), TMS-Cl, Hünig Base or K_2CO_3, 80°C, 5h, 80%.

Examples

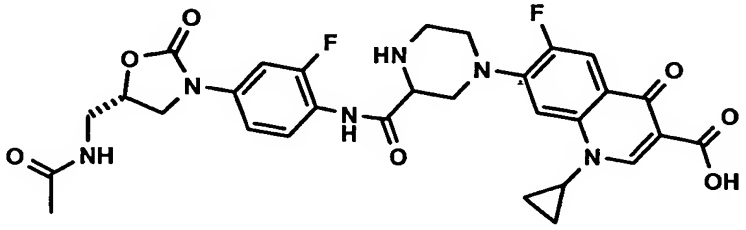
EXAMPLE 1: 7-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



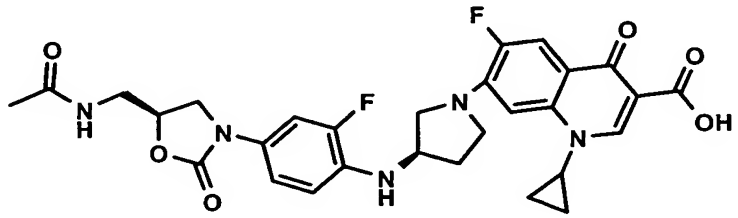
EXAMPLE 2: 9-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



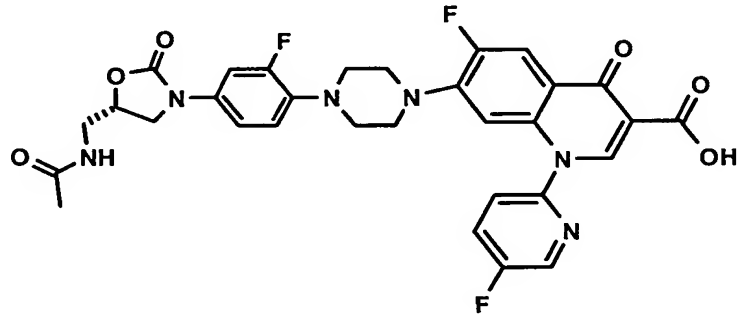
EXAMPLE 3: 7-((3R,S)-3-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylcarbamoyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



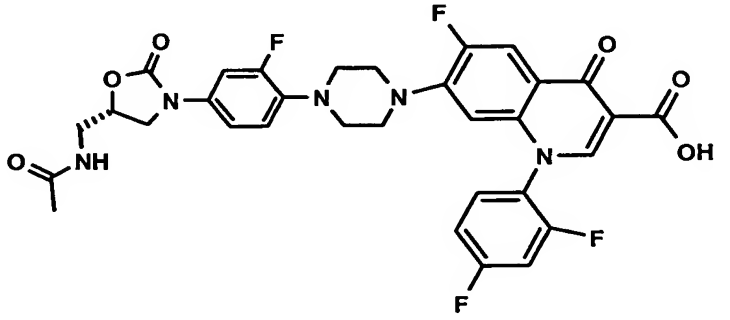
EXAMPLE 4: 7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-1-carboxylic acid.



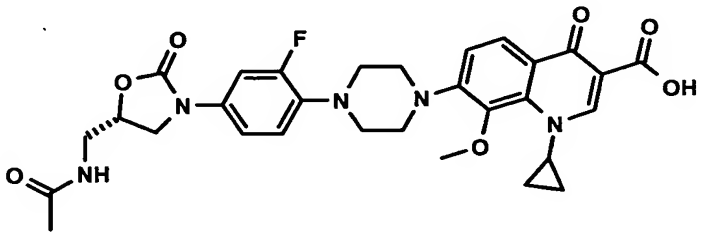
EXAMPLE 5: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-1-(5-fluoro-pyridin-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



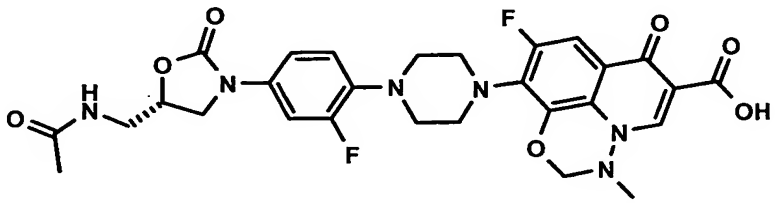
EXAMPLE 6: 7-(4-{(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



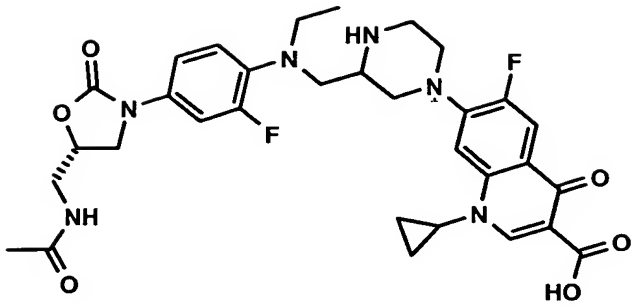
EXAMPLE 7: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclo-propyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



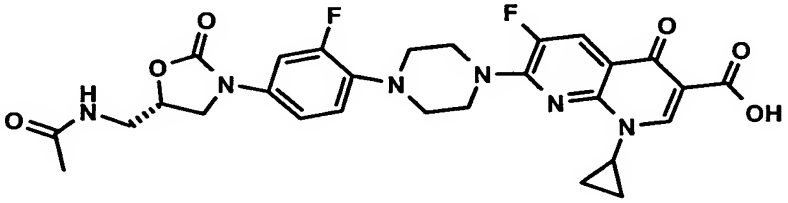
EXAMPLE 8: 9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3,3a-diaza-phenalene-5-carboxylic acid:



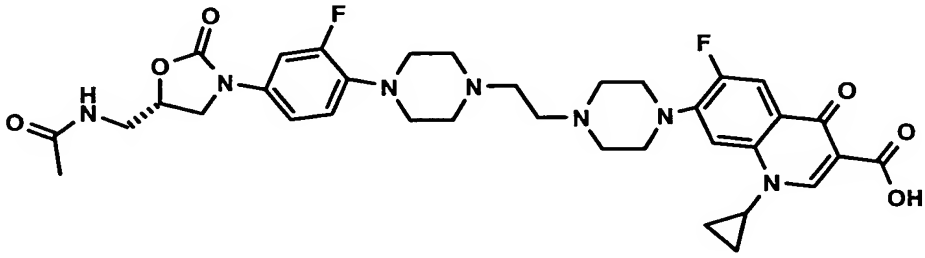
EXAMPLE 9: 7-{(3RS)-3-[({4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-ethyl-amino)methyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



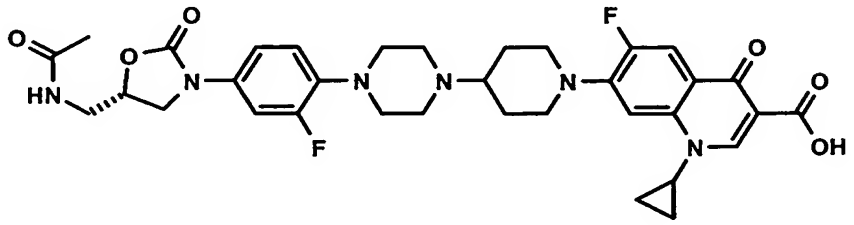
EXAMPLE 10: 7-(4-{[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



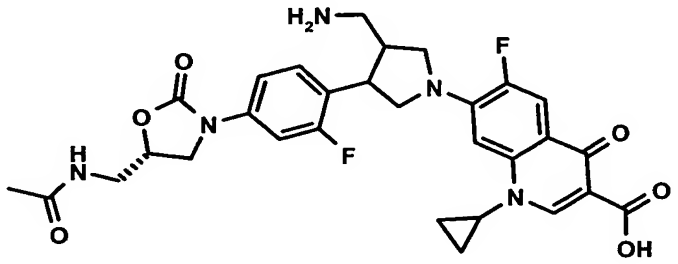
EXAMPLE 11: 7-{4-[2-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-ethyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



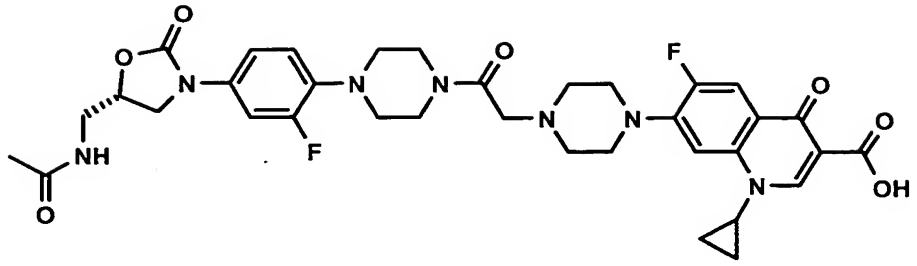
EXAMPLE 12: 7-[4-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



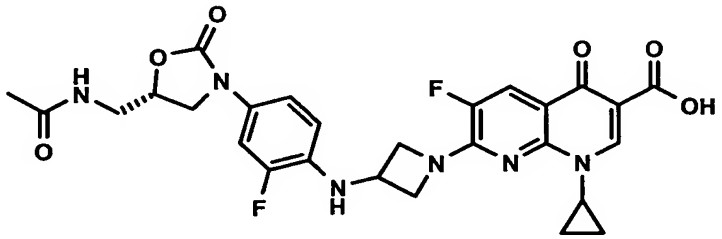
EXAMPLE 13: 7-[(3R, 4R) and (3S, 4S)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid.



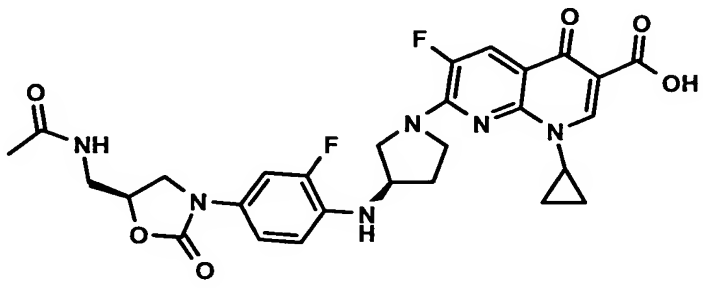
EXAMPLE 14: 7-{4-[2-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid:



EXAMPLE 15: 7-(3-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-azetidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

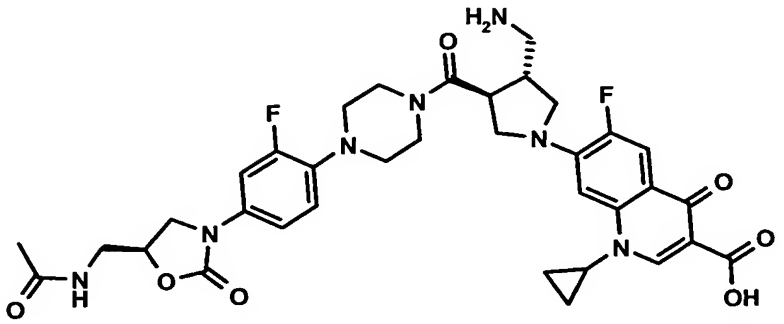


EXAMPLE 16: 7-[(3R)-3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:

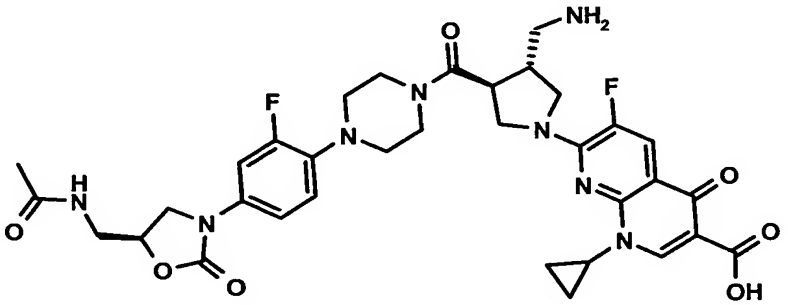


EXAMPLE 17: 7-[(3R, 4S) and (3S, 4R)-3-(-4{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-

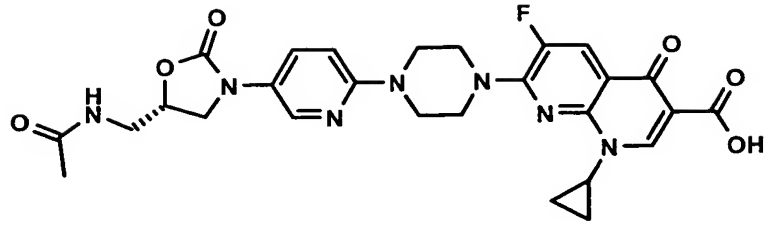
phenyl}piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline carboxylic acid



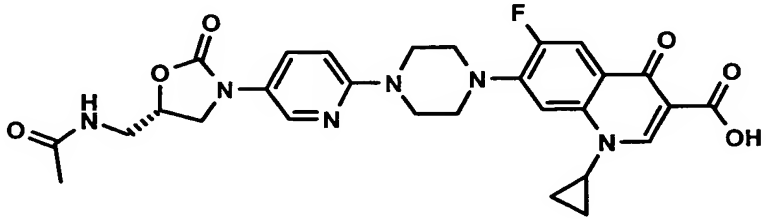
EXAMPLE 18: 7-[(3R, 4S) and (3S, 4R)-3-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazine-1-carbonyl)-4-aminomethyl-pyrrolidin-1-yl)1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



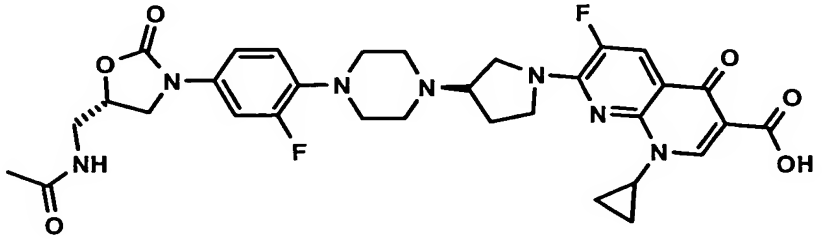
EXAMPLE 19: 7-(4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-1-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



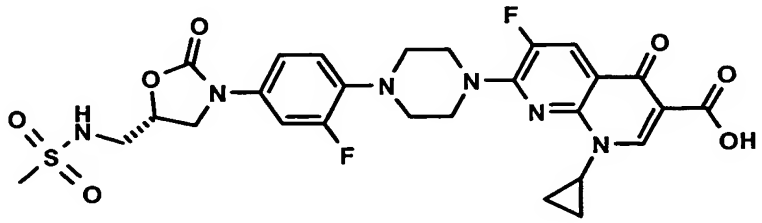
EXAMPLE 20: 7-(4-{5-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-pyridin-2-yl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



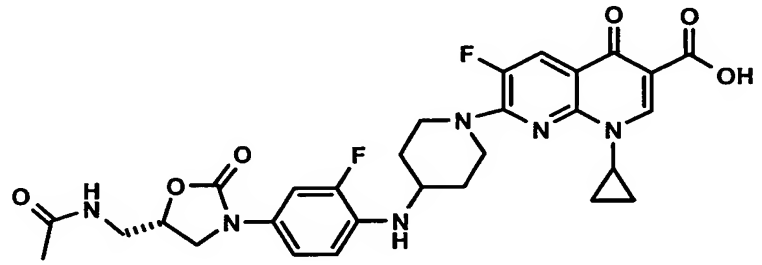
EXAMPLE 21: 7-[(3R)-3-(4-{4[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



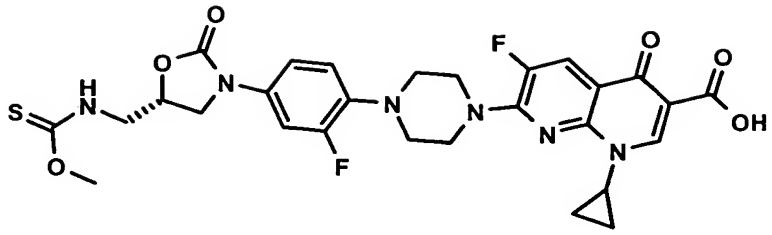
EXAMPLE 22: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5R)-5-(methansulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.



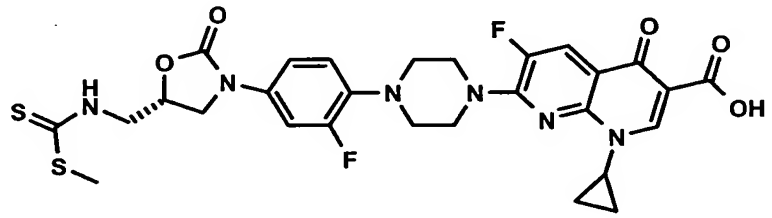
EXAMPLE 23: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylamino}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



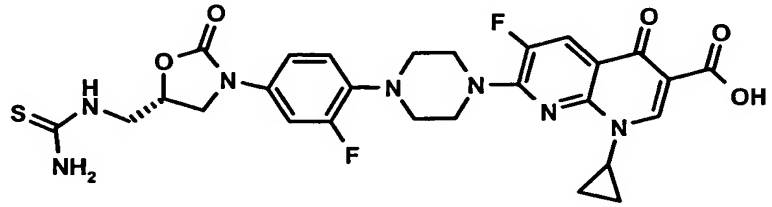
EXAMPLE 24: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[(5S)-5-(methoxythiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:



EXAMPLE 25: 1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-((5S)-5-(methylsulfanylthiocarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4dihydro-[1,8]naphthyridine-3-carboxylic acid:

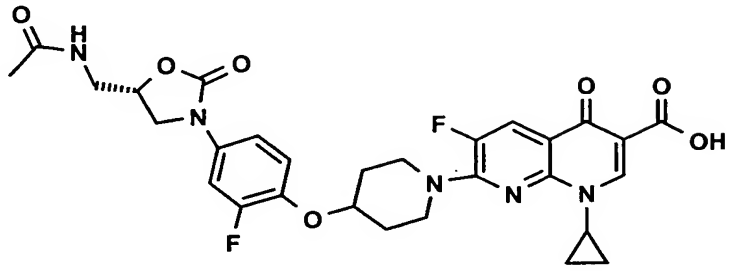


EXAMPLE 26: 1-Cyclopropyl-6-fluoro-{4-[2-fluoro-4-{(5S)-2-oxo-5-thioureidomethyl-oxazolidin-3-yl}-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

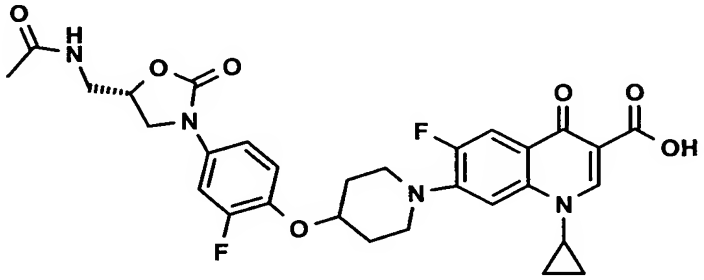


EXAMPLE 27: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-1-

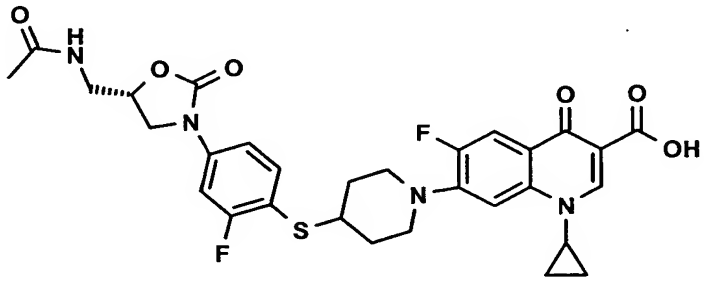
cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



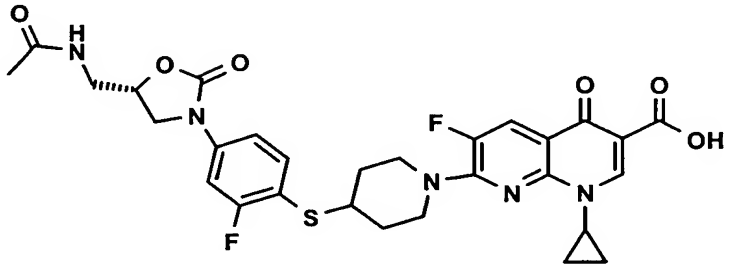
EXAMPLE 28: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



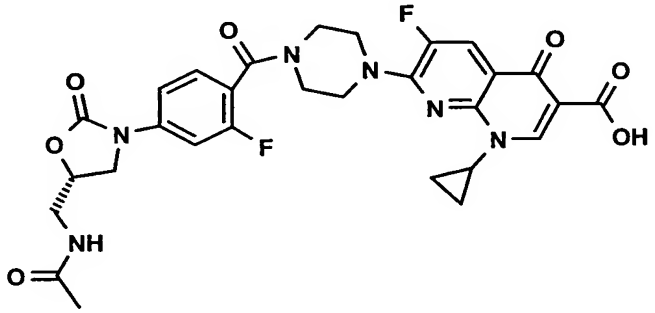
EXAMPLE 29: 7-(4-{4-[5(S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylsulfanyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



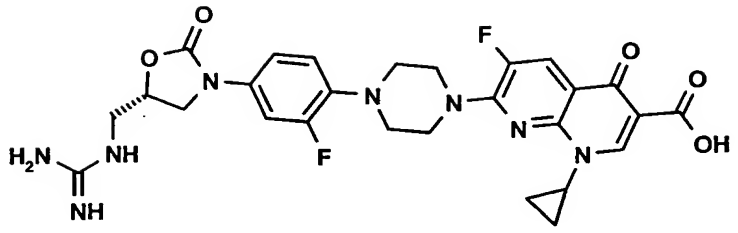
EXAMPLE 30: 7-(4-{4-[5(S)-5(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylsulfanyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



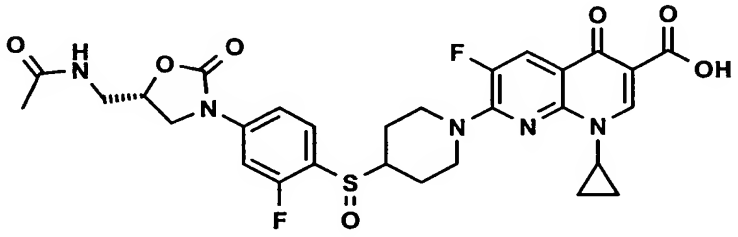
EXAMPLE 31: 7-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-benzoyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



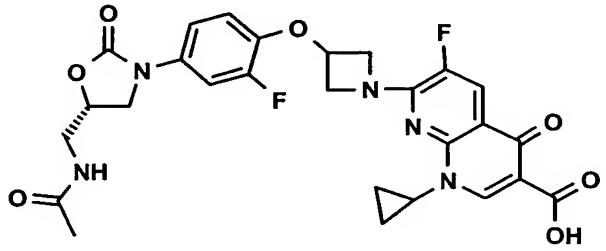
EXAMPLE 32: 1-Cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-guanidinomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



EXAMPLE 33: 7-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-benzenesulfinyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



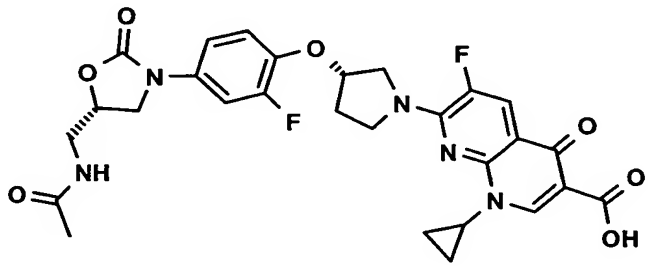
EXAMPLE 34: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-azetidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



A suspension of 100 mg N-{(5S)-3-[4-(Azetidin-3-yloxy)-3-fluoro--phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 323.32, 0.31 mmol), 73 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.25 mmol) ,0.066 ml

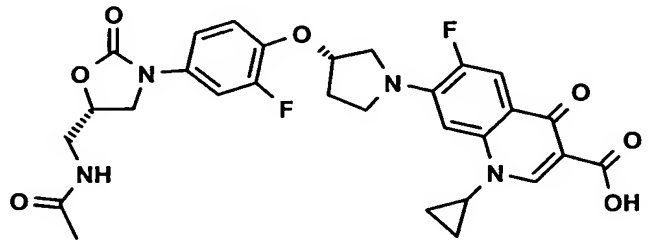
trimethylchlorosilane (MW:108.64, d=0.859, 0.51 mmol) and 0.108 ml triethylamine (MW:101.19, d=0.726, 0.77 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 55 mg, 30 %. MS: 570.5 $(M+H)^+$, Method ESI^+. Molecular Weight =570

EXAMPLE 35: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

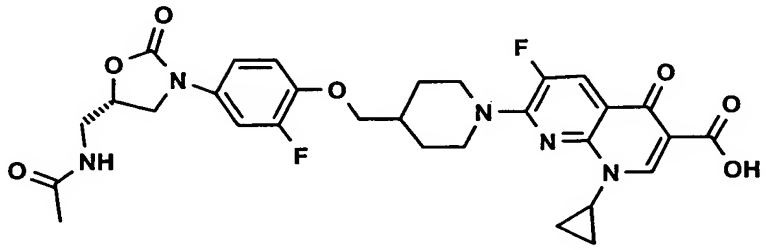


A suspension of 185 mg N-{(5S)-3-[-3-fluoro-4{3-(S)-(pyrrolidin-3-yloxy)}-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (337.35, 0.55 mmol), 141 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.5 mmol) ,0.126 ml trimethylchlorosilane (MW:108.64, d=0.859, 1 mmol) and 0.209 ml triethylamine (MW:101.19, d=0.726, 1.5 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Molecular Weight =584; Yield: 140 mg, 48 %; MS: 584.5 $(M+H)^+$, Method ESI^+.

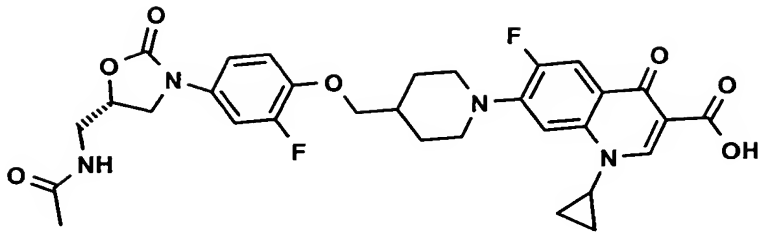
EXAMPLE 36: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



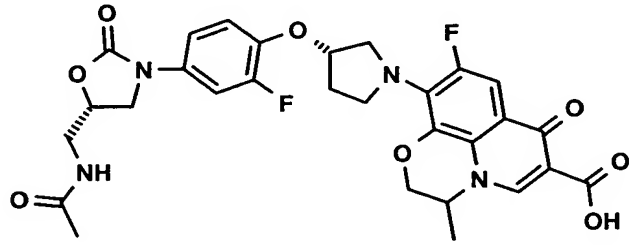
EXAMPLE 37: 7-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



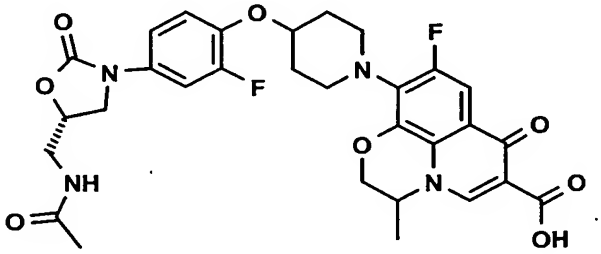
EXAMPLE 38: 7-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



EXAMPLE 39: 9-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

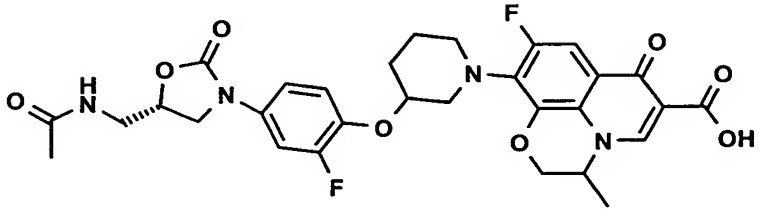


EXAMPLE 40: 9-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

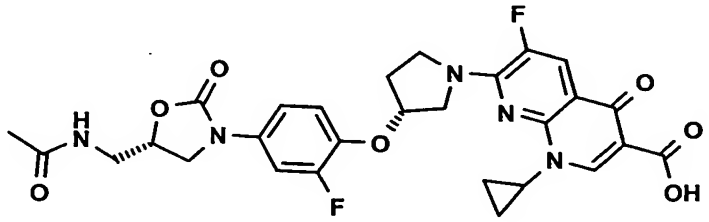


EXAMPLE 41: 9-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-8-

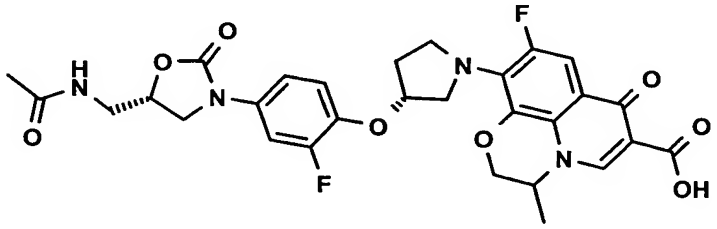
fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



EXAMPLE 42: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

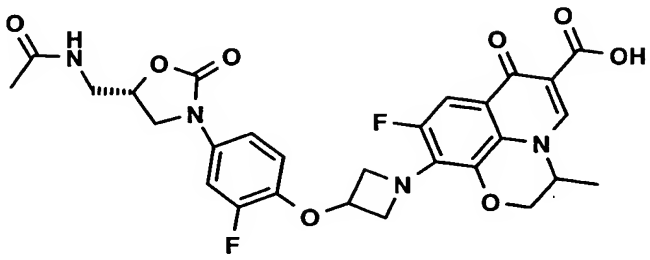


EXAMPLE 43: 9-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

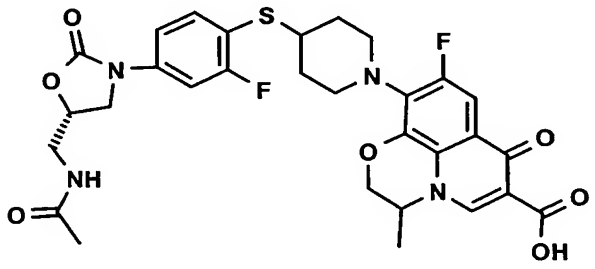


EXAMPLE 44: 9-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-azetidin-1-yl)-8-

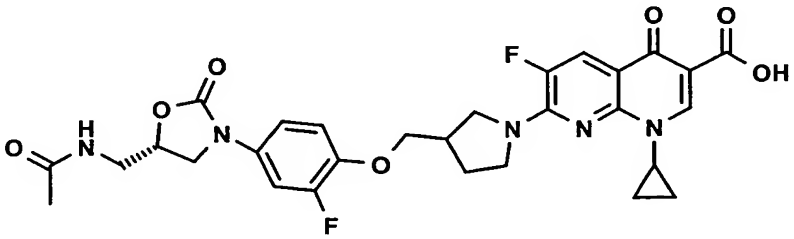
fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



EXAMPLE 45: 9-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenylsulfanyl}-piperidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

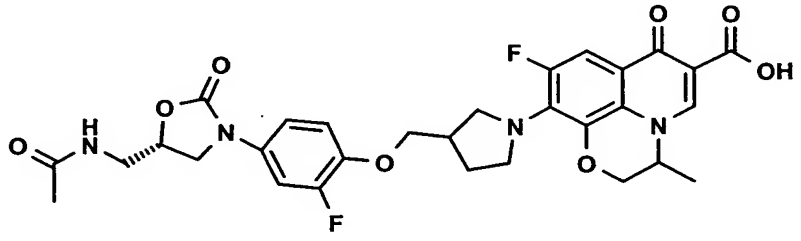


EXAMPLE 46: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



A suspension of 179 mg N-{(5S)-3-[3-fluoro- 4-[3-(RS)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.55 mmol), 141 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.5 mmol), 0.128 ml trimethylchlorosilane (MW:108.64, d=0.859, 1.0 mmol) and 0.200 ml triethylamine (MW:101.19, d=0.726, 1.5 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 241 mg, 81 %. MS: 598.5 $(M+H)^+$, Method ESI^+. Molecular Weight =598.

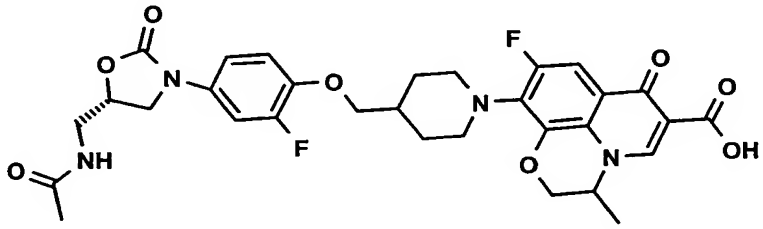
EXAMPLE 47: 9-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



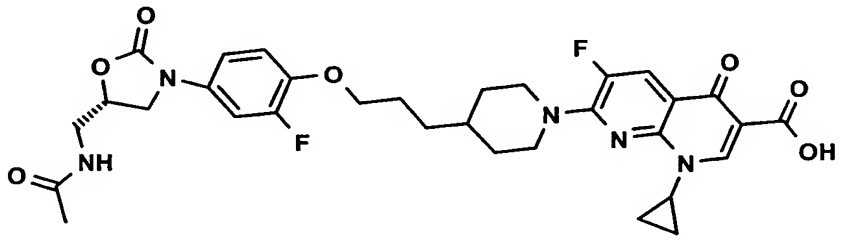
A suspension of 179 mg N-{(5S)-3-[3-fluoro- 4-[3-(RS)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.55 mmol), 140 mg 9-10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxilic acid (MW: 281.21, 0.5 mmol), 0.128 ml trimethylchlorosilane (MW:108.64, d=0.859, 1.0 mmol) and 112 mg 1,4-diazabicyclo[2.2.2]octane (MW:112.18, 1.0 mmol) in 2 ml N-methyl-pyrrolidin-2-one

was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by crystallisation. Yield: 161 mg, 52 %. MS: 613.5 $(M+H)^+$, Method ESI^+. Molecular Weight =613.

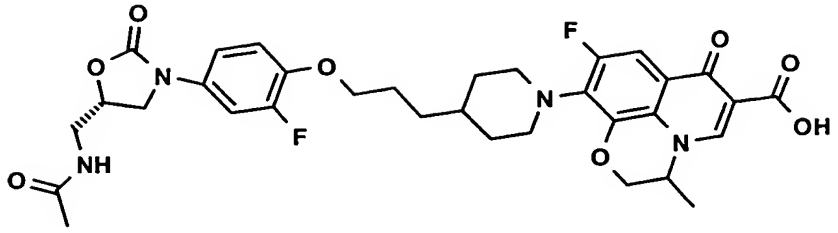
EXAMPLE 48: 9-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



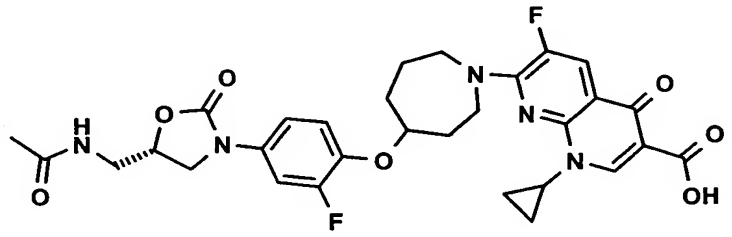
EXAMPLE 49: 7-[4-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-propyl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



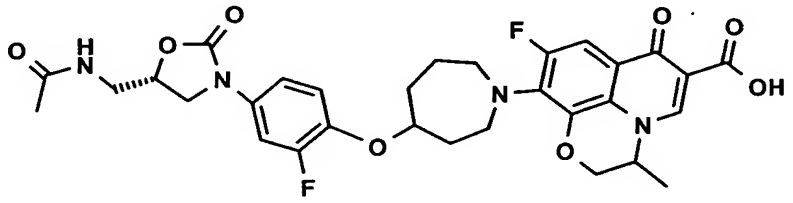
EXAMPLE 50: 9-[4-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-propyl)-piperidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



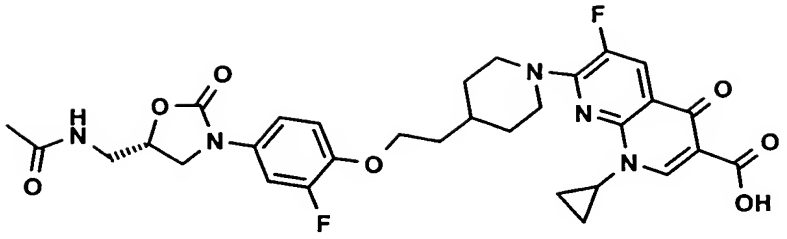
EXAMPLE 51: 7-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



EXAMPLE 52: 9-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-azepan-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:

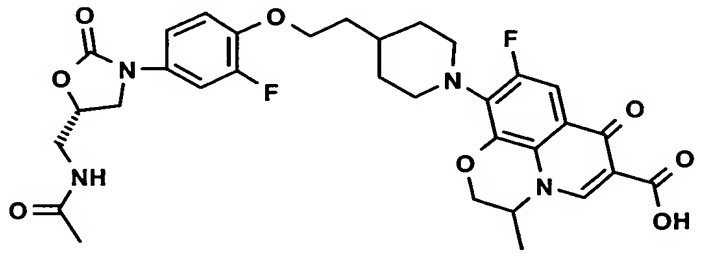


EXAMPLE 53: 7-[4-(2-{4-[(5S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



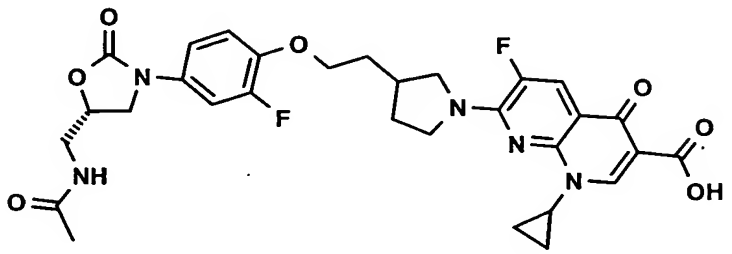
A suspension of 100 mg N-{(5S)-3-[3-fluoro- 4-[4-(piperazin-4-yl-ethoxy)]-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 379.43, 0.263 mmol), 68 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.239 mmol), 0.060 ml trimethylchlorosilane (MW:108.64, d=0.859, 0.47 mmol) and 0.1 ml triethylamine (MW:101.19, d=0.726, 0.71 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 30 mg, 20 %. MS: 626.5 $(M+H)^+$, Method ESI^+. Molecular Weight =626

EXAMPLE 54: 9-[4-(2-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-piperidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



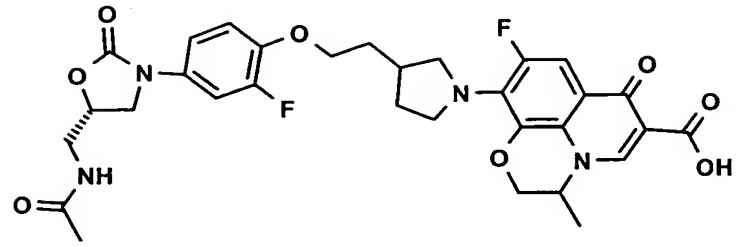
EXAMPLE 55: 7-[3(R,S)-(2-{4-[(5S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-pyrrolidin-

1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

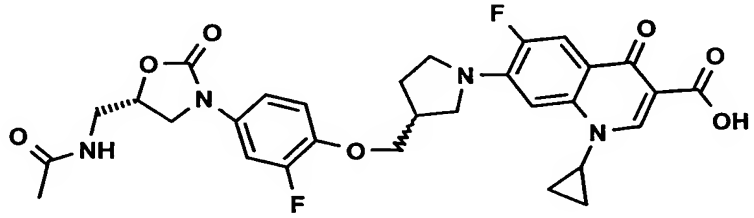


A suspension of 120 mg N-{(5S)-3-[3-fluoro- 4-[4(R,S)-4-(piperazin-4-yl-ethoxy)]-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 365.40, 0.33 mmol), 85 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.3 mmol), 0.075 ml trimethylchlorosilane (MW:108.64, d=0.859, 0.6 mmol) and 0.127 ml triethylamine (MW:101.19, d=0.726, 0.9 mmol) in 3 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, and the residue dissolved in dichloromethane. The organic layer was washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was digested in ethyl acetate, the resulting colourless solid was filtered and dried. Yield: 159 mg, 86 %. Molecular Weight 612.

EXAMPLE 56: 9-[3-(2-{4-[5-(Acetylamino-methyl)- 2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid:



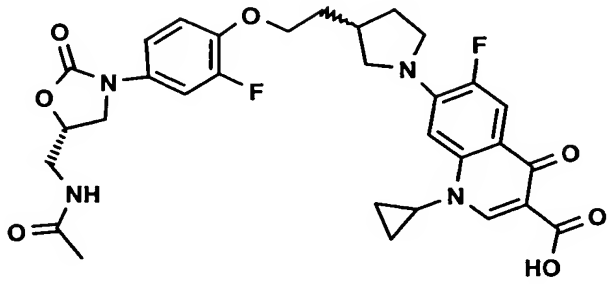
EXAMPLE 57: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



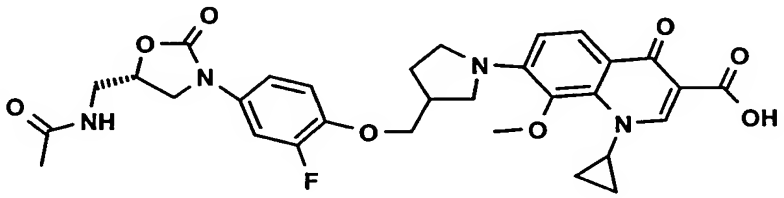
A suspension of 176 mg N-{(5S)-3-[3-fluoro- 4-[3-(RS)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.5 mmol), 205 mg 7-chloro- 6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylato-boron diacetate (MW: 409.56, 0.5 mmol), and 0.341 ml N-ethyldiisopropylamine (MW:129.25, d=0.755, 2 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography and crystallisation from ethanol. Yield: 120 mg, 40 %. MS: 597.5 $(M+H)^+$, Method ESI^+. Molecular Weight =597.

EXAMPLE 58: 7-[3-(2-{4-[5-(Acetylamino-methyl)- 2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-pyrrolidin-1-

yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

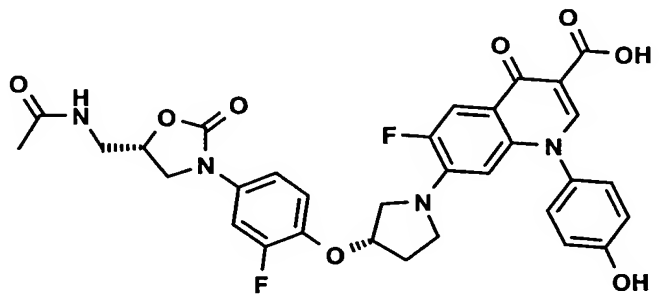


EXAMPLE 59: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

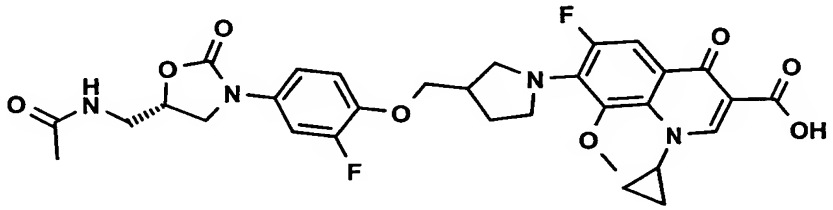


A suspension of 100 mg N-{(5S)-3-[3-fluoro-4-[3-(RS)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.284 mmol), 115 mg 1-cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylatoboron diacetate (MW: 405.14, 0.284 mmol) and 0.097 ml N-ethyldiisopropylamine (MW:129.25, d=0.755, 0.57 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography and crystallisation from ethanol. Yield: 40 mg, 23 %. MS: 609.5 $(M+H)^+$, Method ESI^+. Molecular Weight =609.

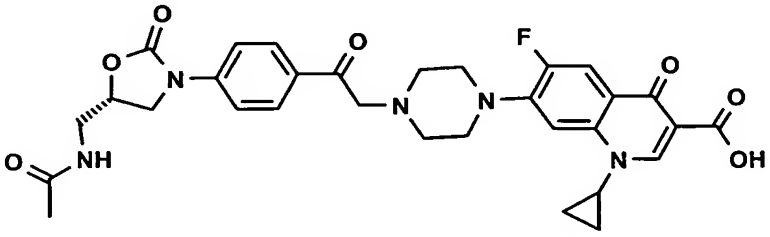
EXAMPLE 60: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-pyrrolidin-1-yl)-6-fluoro-1-(4-hydroxy-phenyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



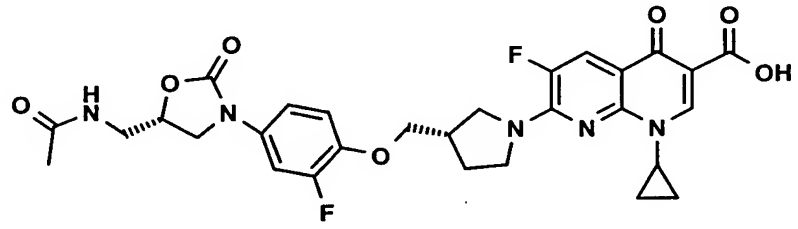
EXAMPLE 61: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:



EXAMPLE 62: 7-[4-(2-{4-[5-(Acetylamino-methyl)- 2-oxo-oxazolidin-3-yl]-phenyl}-2-oxo-ethyl)-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

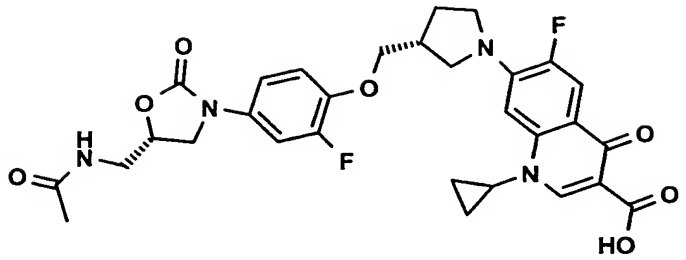


EXAMPLE 63: 7-(3(S)-{4-[5(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



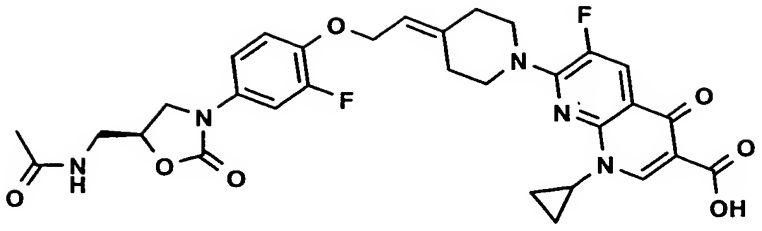
A suspension of 737 mg N-{(5S)-3-[3-fluoro- 4-[3-(S)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 2.1 mmol), 566 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 2 mmol), 0.505 ml trimethyl-chlorosilane (MW:108.64, d=0.859, 4 mmol) and 0.840 ml triethylamine (MW:101.19, d=0.726, 6 mmol) in 15 ml N-methyl-pyrrolidin-2-one was heated under stirring at 150 °C for 2 hrs. The N-methyl-pyrrolidin-2-one was evaporated, and the residue dissolved in dichloromethane. The organic layer was washed with water and brine, dried over Mg sulfate, filtered and the filtrate evaporated. The residue was purified by crystallisation from an ethanol and dichloromethane mixture. Yield: 972 mg, 81 %. MS: 598.5 $(M+H)^+$, Method ESI^+. Molecular Weight 598.

EXAMPLE 64: 7-(3(R)-{4-[5(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

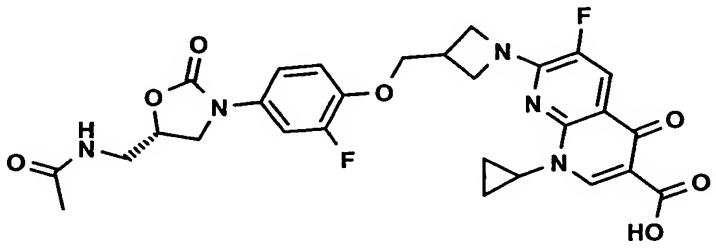


A suspension of 1.228 g N-{(5S)-3-[3-fluoro- 4-[3-(R)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 3 mmol), 1.054 g 7-chloro-6-fluoro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylato-boron diacetate (MW: 409.56, 3 mmol), and 2 ml N-ethyl-diisopropylamine (MW:129.25, d=0.755, 12 mmol) in 30 ml N-methyl-pyrrolidin-2-one was heated under stirring at 150 °C for 2 hrs. The N-methyl-pyrrolidin-2-one was evaporated, and the residue dissolved in dichloromethane. The organic layer was washed with 0.1N HCl and with brine, dried over Mg sulfate, filtered and the filtrate evaporated to dryness. The residue was digested in warm ethyl acetate, the crystals filtered (DC1). The solid was crystallised from ethanol. Yield: 728 mg, 41 %. MS: 597.5 $(M+H)^+$, Method ESI^+. Molecular Weight 597.

EXAMPLE 65: 7-[4-(2-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethylidene)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:



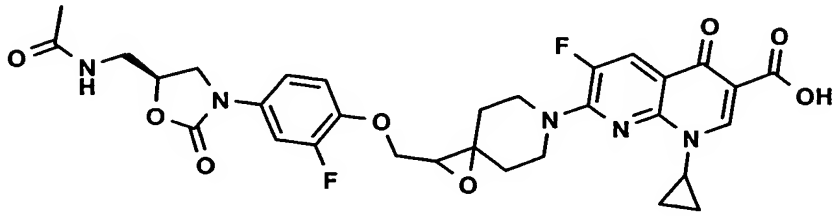
EXAMPLE 66: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-azetidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



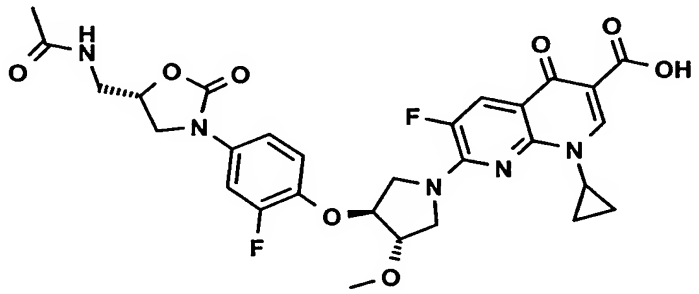
A suspension of 179 mg N-{(5S)-3-[4-(Azetidin-3-ylmethoxy)-3-fluoro--phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 337.35, 0.31 mmol), 100 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.25 mmol), 0.134 ml trimethylchlorosilane (MW:108.64, d=0.859, 1.059 mmol) and 0.197 ml triethylamine (MW:101.19, d=0.726, 1.41 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 82 mg, 40 %. MS: 583.5 $(M+H)^+$, Method ESI^+. Molecular Weight =584

EXAMPLE 67: 7-(2-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-oxa-6-aza-

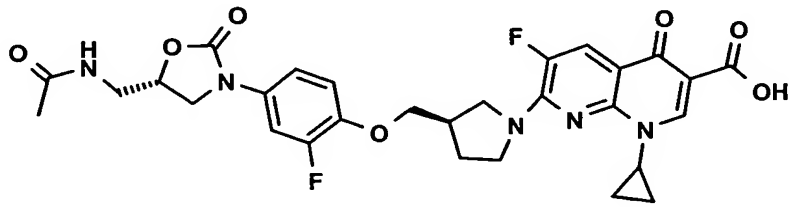
spiro[2.5]oct-6-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



EXAMPLE 68: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-4-methoxy-pyrrolidin-1-yl)-1-cyclo-propyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]-naphthyridine-3-carboxylic acid:

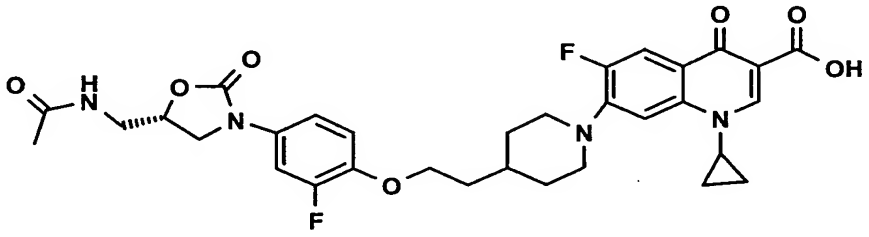


EXAMPLE 69: 7-(3(R)-{4-[5(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

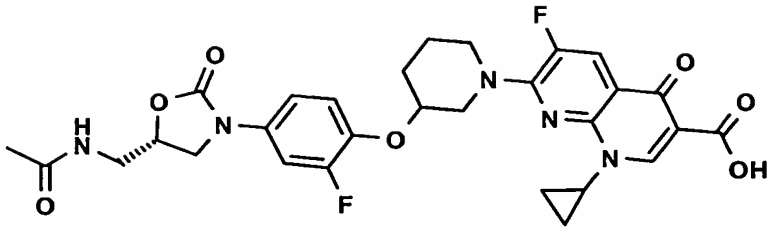


A suspension of 150 mg N-{(5S)-3-[3-fluoro-4-[3-(R)-(pyrrolidin-3-ylmethoxy)]-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.42 mmol), 100 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.35 mmol), 0.147 ml trimethyl-chlorosilane (MW: 108.64, d = 0.859, 1.16 mmol) and 0.216 ml triethylamine (MW:101.19, d=0.726, 1.54 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 150 mg, 60 %. MS: 598.5 $(M+H)^+$, Method ESI^+. Molecular Weight 598.

EXAMPLE 70: 7-[4-(2-{4-[5-(Acetylamino-methyl)- 2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-ethyl)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

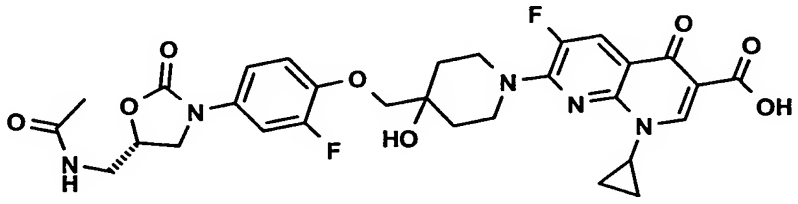


EXAMPLE 71: 7-(3-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxy}-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:



A suspension of 100 mg N-{(5S)-3-[3-fluoro-4-{3-(RS)-piperidin-3-yloxy}-phenyl]-2-oxo-oxazolidin-5-yl methyl}-acetamide (MW: 351.38, 0.28 mmol), 67 mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-Naphthyridine-3-carboxylic acid (MW: 282.66, 0.23 mmol), 0.060 ml trimethylchlorosilane (MW:108.64, d=0.859, 0.47 mmol) and 0.10 ml triethylamine (MW:101.19, d=0.726, 0.71 mmol) in 2 ml N-methyl-pyrrolidin-2-one was heated under stirring in a micro wave oven at 150 °C for 7 min. The N-methyl-pyrrolidin-2-one was evaporated, the residue was purified by chromatography. Yield: 60 mg, 42 %. MS: 598.5 $(M+H)^+$, Method ESI^+.

Example 72: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: (4-Benzyloxy-3-fluoro-phenyl)-carbamic acid benzyl ester:

A solution of 34.9g 1-benzyloxy-2-fluoro-4-nitro-benzene (WO03064413) (MW:247.28, 141mmol) and 340mg platine 5% on activated carbon in 350ml ethyl acetate was stirred under hydrogen at rt and normal pressure. The reaction was monitored by HPLC and was complete after twenty hours. The catalyst was filtered over a glas fibre filter, and the filtrate evaporated under reduced pressure to dryness. The oily residue was dissolved in 500ml acetone and treated with 250ml of a saturated solution of sodium bicarbonate and 17.5g of sodium bicarbonate (MW: 84.01, 208mmol). The mixture was cooled to 5°C and treated drop wise with 26.08g of benzyl chloroformate (MW:170.59, 152mmol). The reaction was allowed to stirred at room temperature for two hours and monitored by TLC (hexane/ethyl acetate 3:1). The acetone was evaporated, the residue diluted with 500ml water, and the solid filtered off. The crystals were washed with 500ml water and dried. Yield: 48.05g, 95.8%. MS: 352.5 $(M+H)^+$, 350.8, $(M-H)^-$. Method ESI^+, ESI^-.

Step 2: (5R)-3-(4-benzyloxy-3-fluoro-phenyl)-5-hydroxy-methyl-oxazolidin-2-one:

A stirred solution of 17.5g (4-benzyloxy-3-fluoro-phenyl)-carbamic acid benzyl ester (MW: 351.38, 50mmol) in 30ml of dry tetrahydrofurane was cooled to -78°C with a dry ice/acetone bath. 22.8ml of a 2.3M n-butyl-lithium solution in n-hexane (52.5mmol) was added drop wise and the reaction mixture stirred at - 78 °C for 15 min. 7.92g *R(-)*-glycidyl butyrate (MW: 144.17, 60mmol) were added and the reaction was allowed to warm up to room temperature. The reaction was monitored by HPLC, quenched with a saturated ammonium chloride solution and diluted with 100ml of ethyl acetate. The organic layer was washed

with 200ml water and 200ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was crystallized from 200ml of a 1/1-ethyl acetate/hexane mixture. The solid was collected and recrystallized from 150ml of a 9/1 ethyl acetate/dichloromethane mixture. The colorless crystals were collected and dried. Yield: 10.4-g, 65.5%. MS: 318.1 $(M+H)^+$. Method ESI^+.

Step 3: (5S)-5-azidomethyl-3- (4-benzyloxy-3-fluoro-phenyl)-oxazolidin-2-one:

A solution of 10g (5R)-3-(4-benzyloxy-3-fluoro-phenyl)-5-hydroxymethyl-oxazolidin-2-one (MW: 317.32, 31.51mmol) and 4.78g triethylamine (MW: 101.19, 47.26mmol) in 300ml dichloromethane was treated under stirring at 10°C with 4.32g of methane sulfonyl chloride (MW: 114.55, 37.82mmol). The reaction was stirred at room temperature for one hour and monitored by TLC (ethyl acetate: hexane 1:1). The reaction mixture was quenched with 100ml water and the organic layer washed with 100ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 100ml dimethylformamide, 5.12g sodium azide (MW: 65.01, 78.7mmol) and a catalytic amount of tetrabutyl ammonium iodide were added. The suspension was stirred at 90 °C over night. The reaction was monitored by HPLC. The dimethylformamide was evaporated under reduced pressure, the residue dissolved in 200ml dichloromethane and the organic layer washed successively with 100ml water and 100ml brine. The dichloromethane solution was dried over magnesium sulfate, filtered, and the filtrate evaporated under reduced pressure. The residue was crystallized from 150ml of a 1/1 mixture of

ethyl acetate: hexane. The crystals were collected to afford an off white solid. Yield: 10.4-g, 97%. MS: 343.1 $(M+H)^{+-}$. Method: ESI^+.

Step 4: N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide:

A suspension of 10.4g (5S)-5-azidomethyl-3- (4-benzyloxy-3-fluorophenyl)oxazolidin-2-one (MW: 342.33, 30.38mmol) and 1.5g of palladium 10% on activated carbon in 400ml of a 1:1 methanol:ethyl acetate mixture was stirred at room temperature under hydrogen for two days. The catalyst was filtered off using a glass fibre filter paper and the filtrate evaporated under reduced pressure. The residue was dissolved in 100ml of acetic acid, and treated with 3.72g of acetic anhydride (MW: 102.09, 36.45mmol). The solvent was evaporated under reduced pressure and the residue crystallized from a 1:1 ethyl acetate: hexane mixture to afford an off white solid. Yield: 6.76-g, 83%. MS: 269.4 $(M+H)^+$, 267.3, $(M-H)^-$. Method ESI^+, ESI^-.

Step 5: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid benzylester:

A suspension of 22.72g 1-oxa-6-aza-spiro[2.5]octane-6-carboxylic acid benzyl ester (WO9803507) (MW: 247.29, 92mmol), 21.45g N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 80mmol) and 16.58g potassium carbonate (MW: 138.20, 120mmol) in 150ml dimethylformamide was stirred at 100°C for 7 hours. The reaction was monitored by TLC (dichloromethane / methanol 9:1). The dimethylformamide was evaporated under reduced pressure and the residue was dissolved in 600ml of a 9:1 dichloromethane /methanol

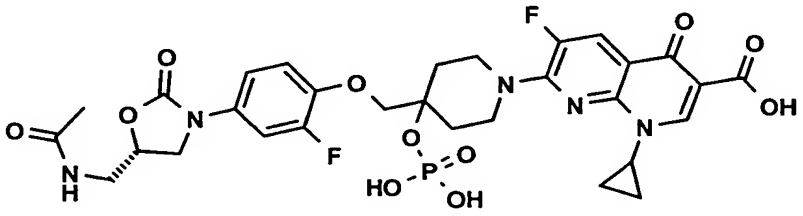
mixture. The organic layer was washed with 400ml water and 400ml brine. The organic layer was dried over magnesium sulfate, filtered, and the filtrate diluted with 250ml ethyl acetate. The mixture was concentrated under reduced pressure to a final volume of 400ml. The slurry was stirred at room temperature over night. The crystals were filtered and washed successively with 150ml ethyl acetate and 100ml pentane. Yield: 31.65 g, 76.7%. MS: 516.8 $(M+H)^+$, Method ESI^+.

Step 6: N- [{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-yl-methoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide:
A suspension of 31g 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluorophenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid benzylester (MW: 515,54 60.13mmol) and 2.5 g of palladium 10% on activated carbon in 310ml methanol and 150ml ethyl acetate was stirred under hydrogen for 4 hrs. The reaction was monitored by TLC (ethyl acetate). The reaction slurry was diluted with 300ml methanol, warmed to 40 °C, and the catalyst filtered off using a glass fibre filter paper. The filtrate was concentrated to 150ml, diluted with 300ml ethyl acetate and concentrated again to 200ml. 200ml of diethyl ether were added, and the suspension was cooled to 0°C under stirring. The solid was collected and dried. Yield: 21.6-g, 94.3%. MS: 382.6 $(M+H)^+$, Method ESI^+.

Step7: 7-(4-{[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid:
A suspension of 71mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW:

282.66, 0.25mmol), 95mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide (MW: 381.40, 0.25mmol) 102mg triethylamine (MW: 101.19, 1.0mmol) and 81mg trimethylchlorsilan (MW: 108.64, 0.75mmol) in 1ml N-methyl-pyrrolidin-2-one was heated at 80°C under stirring for 5 hours. The reaction was monitored by TLC (dichloromethane: methanol 9:1). The N-methyl-pyrrolidin-2-one was evaporated, the residue dissolved in 20ml of a 9:1 dichloromethane : methanol mixture, and the solution washed sequentially with 10ml of 0.1 N aqueous hydrochloric acid and 20ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated. The residue was dissolved in 10ml of a 9:1 dichloromethane: methanol mixture and diluted with 20ml ethyl acetate. The precipitated solid was collected to afford an off white solid. A second crop is obtained by concentration under reduced pressure of the mother liquor. Yield: 100mg, 64%. MS: 628.8 $(M+H)^+$, 626.8. $(M-H)^-$ Method ESI^+, ESI^-.

Example 73: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



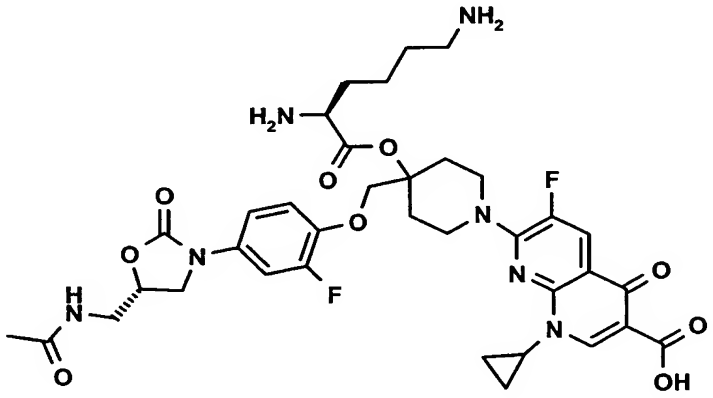
Step 1: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine -3-carboxylic acid:

A suspension of 125mg 7-(4-{[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (MW: 627.60, 0.2mmol) and 42mg tetrazole (MW:70.05, 0.6mmol) in 1ml dichloromethane was treated with 138mg of dibenzyl N,N-diisopropylphosphoramidite (MW: 345.42, 0.4mmol). The original suspension slowly cleared. The solution was stirred at room temperature for two hours and monitored by TLC. (dichloromethane/methanol 9:1). The reaction mixture was cooled to 0°C and treated with a 0.6ml of a 0.5M m-chloroperbenzoic acid solution in dichloromethane. The mixture was stirred for two hours at room temperature and diluted with 20ml dichloromethane. The organic layer was washed successively with 20ml of a saturated aqueous sodium bicarbonate solution and 20ml of brine and dried over magnesium sulfate. The slurry was filtered and the filtrate evaporated under reduced pressure. The residue was purified by chromatography over silica using a 9/1 dichloromethane/methanol mixture as eluent to afford an off white solid. Yield: 158mg, 89%.MS: 889.3 $(M+H)^+$, 887.0 $(M-H)^-$ Method ESI^+, ESI^-.

Step 2: 7-(4-{4-[(5S)-(5-Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine -3-carboxylic acid:

A suspension of 158mg 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine -3-carboxylic acid (MW: 887.84, 0.177mmol) and 20mg of palladium hydroxide 20% on activated carbon in 20ml of a 6/3/1 dichloromethane/methanol/ water mixture was stirred at room temperature under hydrogen for three hours. The catalyst was filtered off using a glass fibre filter paper. The solvents were evaporated under reduced pressure and the residue dissolved in 10ml methanol. The solution was diluted with 20ml water while a white solid precipitated. The solid was collected and dried. Yield: 85mg, 68%. MS: 709.0 $(M+H)^+$, 706.5 $(M-H)^-$ Method ESI^+, ESI^-.

Example 74: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-diamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: 4-{4-[(5S)-(5-Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester:

In analogy of example 72 step 5 by reacting 3.83g 1-oxa-6-aza-spiro[2.5]octane-6-carboxylic acid tert-butyl ester (WO0204462) (MW: 213.28 18mmol), 4.02g N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 15mmol) and 3.1g potassium carbonate (MW: 138.20, 22.5mmol) in 30ml dimethylformamide. Yield: 4.89-g, 67%. MS: 482.6 $(M+H)^+$, Method ESI^+.

Step 2: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidine-1-carboxylic acid tert-butyl ester:

A suspension of 96mg of 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (MW: 481.52, 0.2mmol), 195mg of Z-Lys (Z)-OH (MW: 414.46, 0.4mmol) and 49mg of 4-dimethylaminopyridine (MW: 122.17, 0.4mmol) in 2ml dichloromethane was treated under stirring at room temperature with 115mg N-(3-dimethylaminopropyl)-N´-ethyl-carbodiimid hydrochloride (MW: 191.70, 0.6mmol). The reaction mixture was stirred over night. The mixture was diluted with 20ml ethyl acetate and the organic layer washed successively with 10ml 1 N aqueous hydrochloric acid, 20ml water and 20ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated to dryness. The residue was purified by chromatography on silica, using a 9/1 dichloromethane/ methanol mixture as eluent

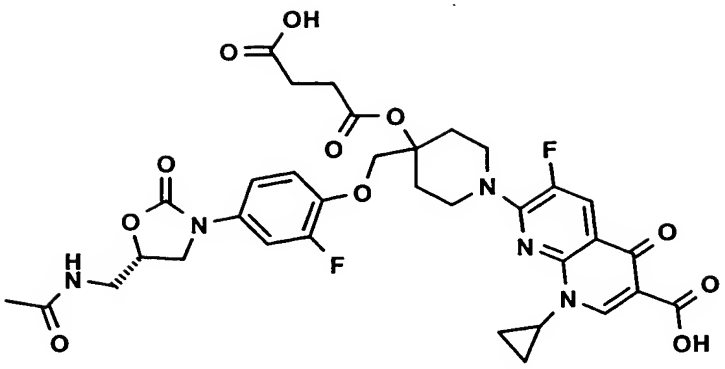
to leave a colorless sticky oil. Yield: 150mg, 88%. MS: 878.8 $(M+H)^+$, Method ESI^+.

Step 3: 2,6-Bis-benzyloxycarbonylamino-hexanoic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester hydrochloride: 200mg of 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidine-1-carboxylic acid tert-butyl ester (MW: 977.97, 0.22mmol) were dissolved in 4ml of a 1.25M dry hydrochloric acid in methanol. The reaction was stirred at 40°C for two hours, and the solvent removed by distillation under reduced pressure to leave a off white solid. Yield: 178mg, quantitative. MS: 778.8 $(M+H)^+$, Method ESI^+.

Step 4: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:
In analogy to example 72 step 7, with 62mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW:282.66, 0.25mmol), 178mg 2,6-bis-benzyloxycarbonylamino-hexanoic acid 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester hydrochloride (MW: 814.31, 0.22mmol), 90mg triethylamine (MW: 101.19, 0.88mmol) and 48mg trimethylchlorsilan (MW: 108.64, 0.44mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 94mg, 42%. MS: 1025.3 $(M+H)^+$, Method ESI^+.

Step 5: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-diamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid: A suspension of 94mg 7-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (MW: 1024.05, 0.091mmol) and 20mg of palladium hydroxide 20% on activated carbon in 20ml of a 6/3/1 dichloromethane/methanol/water mixture was stirred at room temperature under hydrogen for four hours. The catalyst was filtered off using a glass fibre filter paper. The solvents were evaporated under reduced pressure and the residue dissolved in 10ml methanol. The solution was diluted with 20ml water while a white solid precipitated. The solid was collected and dried. Yield: 29mg, 43%. MS: 757.0 $(M+H)^+$, 755.2 Method ESI^+, ESI^-.

Example 75: Succinic acid mono-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl] ester



Step 1: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-tert-butoxycarbonyl-piperidin-4-yl ester benzyl ester:
In analogy of example 74 step 2 with 825mg 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (MW: 481.52, 1.71mmol), 1.07g of succinic acid monobenzyl ester (MW: 208.21, 5.14mmol) and 0.63g of 4-dimethylaminopyridine (MW: 122.17, 5.1mmol) in 10ml dichloromethane was treated under stirring at room temperature with 1.3g N-(3-dimethylaminopropyl)-N´-ethyl-carbodiimid HCl (MW: 191.70, 6.8mmol). Yield: 820mg, 70%. MS: 673.3 $(M+H)^+$, Method ESI^+.

Step 2: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester benzyl ester:
820mg of succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-tert-butoxy-carbonyl-piperidin-4-yl ester benzyl ester (MW: 671.72, 1.23mmol) were dissolved in 4ml of trifluoro acetic acid. The reaction mixture was stirred at room temperature for one hour. The solvent was evaporated, the

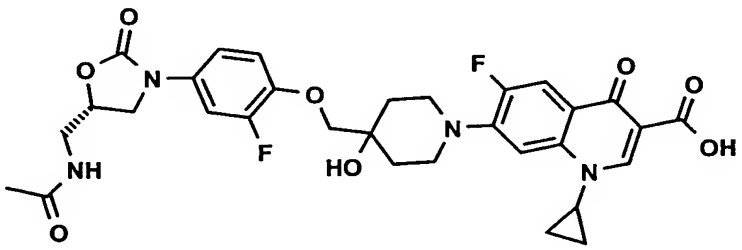
residue dissolved in 30ml of a 9/1 dichloromethane/methanol mixture and the organic layer washed successively with 30ml of a saturated aqueous sodium bicarbonate solution and 30ml of brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was purified by chromatography over silica, using a 95/5 dichloromethane/ methanol mixture with 2% triethylamine as eluent. Yield: 420mg, 60%. MS: 572.7 $(M+H)^+$, Method ESI^+.

Step 3: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl ester benzyl ester:
In analogy to example 72 step 7, with 113mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW:282.66, 0.4mmol), 230mg succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester benzyl ester (MW: 571.60, 0.4mmol), 161mg triethylamine (MW: 101.19, 1.6mmol) and 87mg trimethylchlorsilan (MW: 108.64, 0.8mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 25mg, 7.6%. MS: 819 $(M+H)^+$, 817.8, Method ESI^+, ESI^-.

Step 4: Succinic acid mono-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl] ester:
In analogy to example 74 step 5 with 22mg succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-

2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl ester benzyl ester (MW: 817.80, 0.026mmol) and 2mg of palladium hydroxide 20% on activated carbon in 20ml of a 1/1 tetrahydrofuran/ methanol mixture. Yield: 16mg, 81%. MS: 729 $(M+H)^+$, 727 $(M+H)^-$, Method ESI^+, ESI^-.

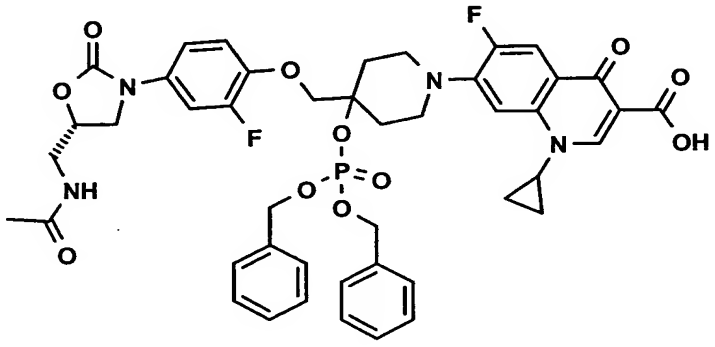
Example 76: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



A solution of 60g N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide. ($C_{18}H_{24}FN_3O_5$, MW: 381.40 0.157 mole) and 26.87ml of ethyl diisopropylamine (MW: 129.25, 0.157 mole) in 300ml N-methyl-pyrrolidin-2-one was treated with 67.81g (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.165 mole) and the mixture was stirred at 80°C for 5 hours. The N-methyl-pyrrolidin-2-one was evaporated under reduced pressure and residue was dissolved in 300ml of methanol. Anhydrous hydrogen chloride was bubbled through the solution at 10 °C for 30 minutes. The solution was stirred at room temperature

while a yellow solid precipitated. The conversion of the boron complex to the free acid was monitored by HPLC. The mixture was diluted with 300ml ethyl acetate. The solid was filtered and washed with 100ml of 8/2 ethyl acetate/methanol and 100ml of ethyl acetate. The yellow solid was dried to leave 86.4 g of a yellow solid. The solid was dissolved in 200ml dimethylsulfoxyde at 40 °C, and the yellow solution was added under stirring to 1000ml water. The yellow solid was collected, washed with water and dried. Yield: 73g, 74.5%. MS: 627.8 $(M+H)^+$, 625.8 $(M+H)^-$, Method ESI^+, ESI^-.

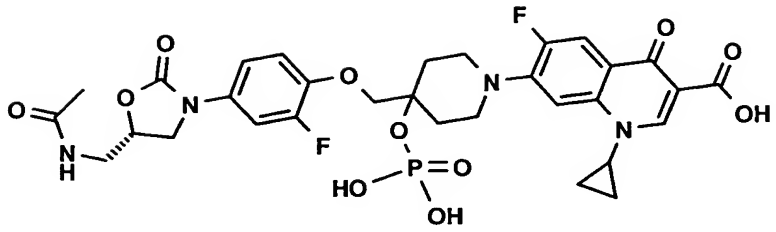
Example 77: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



A suspension of 35g 7-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (MW: 626.61, 55.85mmol) and 6,45g tetrazole (MW: 70.05, 92.15mmol) in 700ml dichloromethane was treated at room temperature under

stirring with a solution of 31.8g dibenzyldiisopropylphosphoramidit (MW: 345.42, 92.15mmol) in 20ml dichloromethane. The reaction was monitored by TLC (dichloromethane/methanol 9:1). The reaction was stirred for one hour and the mixture was washed at 0°C with 200ml 1N aqueous hydrochloric acid and 100ml of a saturated sodium bicarbonate solution. The water layer were backwashed with 200ml dichloromethane. The combined organic layer were concentrated to 500ml and treated at roomtemperature with 13,2ml of a 70 % ter-butyl hydroperoxid solution in water (MW:90.12, 95mmol). The reaction was stirred for 30 min, diluted with 500ml dichloromethane and the organic layer washed with 200ml 1N aqueous hydrochloric acid and with 300ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 400ml dichloromethane and diluted with 400ml N-hexane. The mixture was concentrated (300-mbar, 40°C bath temperature) to a volume of 400ml. The sticky oil was decanted and dissolved in 400ml of refluxing methanol. The solution was concentrated to 300ml under reduced pressure and stirred over night at RT. The slurry was cooled to 0°C and the solid collected. Yield: 27.60g, 55.6%. MS: 888.3 $(M+H)^+$, 885.8 $(M+H)^-$, Method ESI^+, ESI^-.

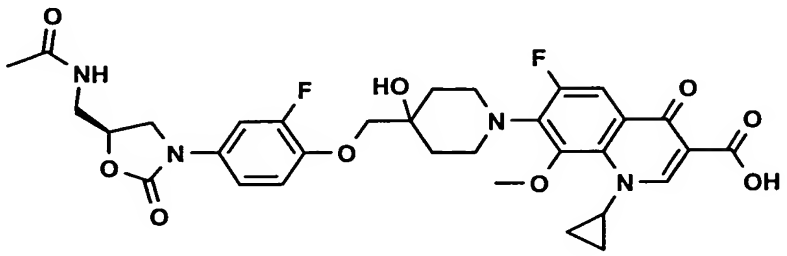
Example 78: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



27g 7-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (MW: 886.85, 30.44mmol) were suspended in 600ml acetonitrile and treated with 53ml of a 33% solution of anhydrous hydrobromic acid in acetic acid. The yellow suspension was diluted with 150ml of acetic acid and was heated to 45°C. The reaction was monitored by HPLC/MS and was complete after 3 hours. The sticky suspension was added to 1.5 L of water under stirring. The off white crystals were collected, washed with 300ml water, 150ml ethanol and 150ml ether. The solid was suspended in 1.3L water and treated with 35ml (35mmol) of a 1M aqueous sodium hydroxide solution. The solid dissolved, and the brown-yellow solution was treated with 15 g of activated charcoal and filtered. The filtrate was extracted with 3 portions of 200ml of a 95/5 dichloromethane/ methanol mixture. The water layer was treated with 40ml of 1 M HCl solution and the product crystallized by stirring. The solid was collected and dried. Yield: 17.3-g, 80.4 %. MS: 609.7 $(M+H)^+$, 607.8 $(M+H)^-$, Method ESI^+, ESI^-.

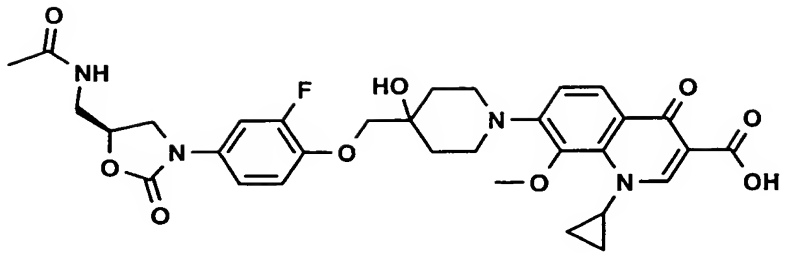
Example 79: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-

piperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



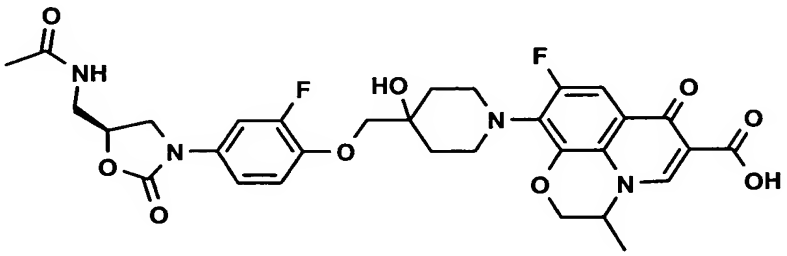
In analogy to example 76 with 114mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide. (MW: 381.40 0.3mmol), 127mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid diacetylborate (Sakurai, Nobuhiro; Sano, Mitsuharu; Hirayama, Fumihiro; Kuroda, Tsuyoshi; Uemori, Satoru; Bioorg.Med.Chem.Lett.; 8; 16; 1998; 2185-2190) (MW: 423.137, 0.3mmol) and 38mg of ethyl diisopropylamine (MW: 129.25, 0.3mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 137 mg, 69.5 %. MS: 658.2 $(M+H)^+$, 655.8 $(M+H)^-$, Method ESI^+, ESI^-.

Example 80: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 76 with 114mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}]-acetamide. (MW: 381.40 0.3mmol), 121mg of 1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (WO03032962) (MW: 405.15, 0.3mmol) and 77mg of ethyl diisopropylamine (MW: 129.25, 0.6mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 117mg, 61.2 %. MS: 639.8 $(M+H)^+$, 637.5 $(M+H)^-$, Method ESI^+, ESI^-.

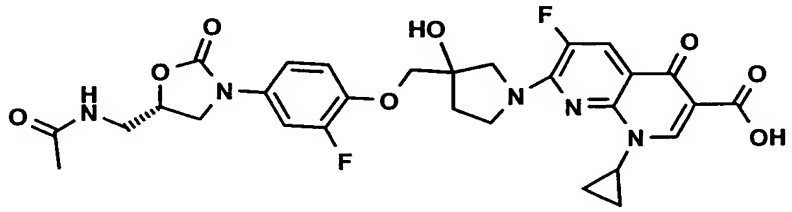
Example 81: 9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



A solution of 140mg of 9-10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxilic acid (MW: 281.22, 0.5mmol), 191mg of N-[{(5S)-

3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}]-acetamide (MW: 381.40, 0.5mmol), and 129mg of ethyl diisopropylamine (MW: 129.25, 1mmol) was stirred at 80°C in 1ml of N-methyl-pyrrolidin-2-one for 24 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol and treated with 10ml of a 1.2 M anhydrous hydrogen chloride solution in methanol. The methanol was evaporated and the residue digested in ethyl acetate. The solid was collected and crystallized twice from a dichloromethane/ethanol mixture. Yield: 88mg, 27 %. MS: 643.7 $(M+H)^+$, 641.5 $(M+H)^-$, Method ESI^+, ESI^-.

Example 82: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: 1-Oxa-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester:

A solution 3-methylen-pyrrolidine-1-carboxylic acid benzyl ester (WO9624593) in 5ml of dichloromethane was treated with 2.16g sodium bicarbonate (MW: 84.01 26.28mmol) and 2.47g of 80% m-chlor-perbenzoic acid (MW: 172.57, 11.48mmol).The reaction mixture was stirred at room temperature for three hours. The reaction mixture was diluted with 20ml of a saturated aqueous sodium

sulfite solution and 45ml of dichloromethane. The organic layer was successively washed with 30ml of an aqueous saturated sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate. The residue was purified by chromatography on silica (1/1 ethyl acetate/n-hexane) to afford a off white solid. Yield: 440mg, 57 %. MS: 234.1$(M+H)^+$, Method ESI^+.

Step 2: 3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidine-1-carboxylic acid benzyl ester:
A solution of 420mg of N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 1.56mmol) in 2ml dimethylformamide was treated with 83mg sodium hydride. The suspension was stirred for one hour at room temperature. A solution of 440mg 1-oxa-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (MW: 233.26, 1.88mmol) in 1ml DMF was added and the mixture was stirred at 70°C for three hours. The dimethylformamide was evaporated under reduced pressure and the residue was purified by chromatography over silica (95/5 dichloromethane/methanol mixture with 1% ammonia) to afford an off white powder. Yield: 630mg, 80 %. MS: 502.5 $(M+H)^+$, Method ESI^+.

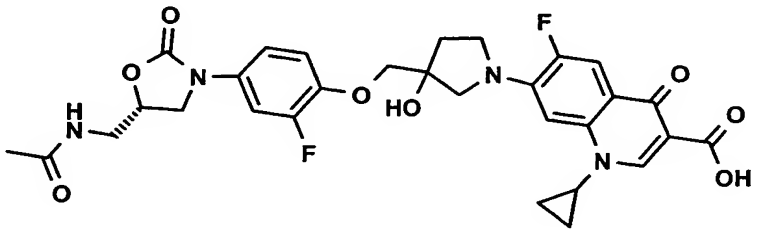
Step 3: N-{(5S)-3-[3-Fluoro-4-(3-hydroxy-pyrrolidin-3-yl-methoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide:
A suspension of 660mg 3-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidine-1-carboxylic acid benzyl ester (MW: 501.51, 1.31mmol) and 20mg palladium 10% on activated carbon in 20ml of a 1/1 ethyl acetate / methanol mixture was stirred for twelve hours under hydrogen. The catalyst was

filtered on a glass fiber filter paper and the filtrate evaporated under reduced pressure to afford a colorless oil. Yield: 400mg, 83.2 %. MS: 368.4 $(M+H)^+$, Method ESI^+.

Step 4: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

In analogy to example 72, step 7 with 39mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW: 282.66, 0.24mmol), 99mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.24mmol) 101mg triethylamine (MW: 101.19, 1.0mmol) and 80mg trimethylchlorsilan (MW: 108.64, 0.75mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 70mg, 46 %. MS: 614.7$(M+H)^+$, 612.7 $(M+H)^-$, Method ESI^+, ESI^-.

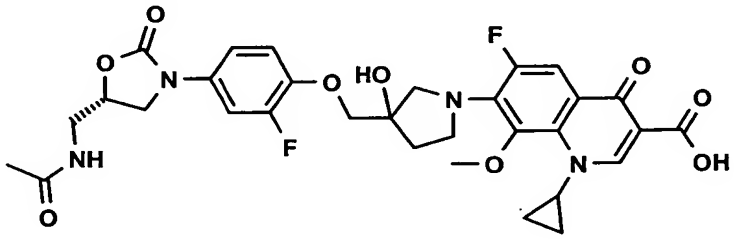
Example 83: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 76 with 106mg N-{(5S)-3-[3-fluoro-4-(3-hydroxypyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.29mmol)

119mg (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.29mmol) and 75mg of ethyl diisopropylamine (MW: 129.25, 0.58mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 19mg, 11 %.MS: 613.5 $(M+H)^+$, 611.5 $(M+H)^-$, Method ESI^+, ESI^-.

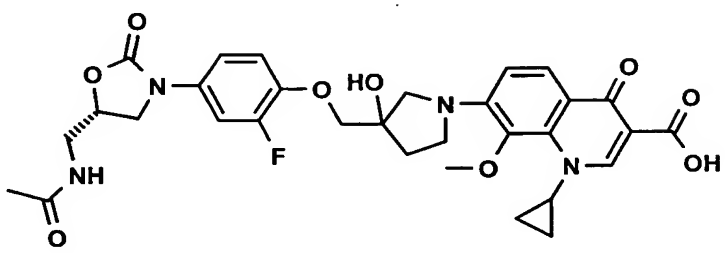
Example 84: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 76 with 143mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 367.38, 0.39mmol), 165mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid diacetylborate (MW: 423.137, 0.39mmol) and 100mg of ethyl diisopropylamine (MW: 129.25, 0.78mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 143mg, 57 %. MS: 643.7 $(M+H)^+$, 641.7 $(M+H)^-$, Method ESI^+, ESI^-.

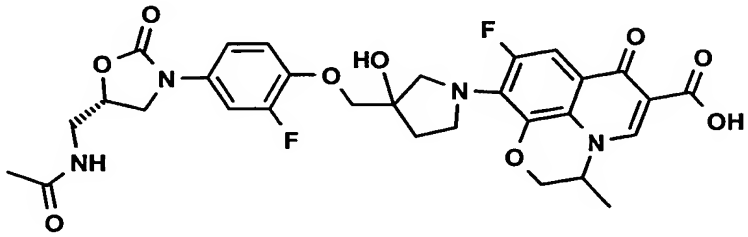
Example 85: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-

pyrrolidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



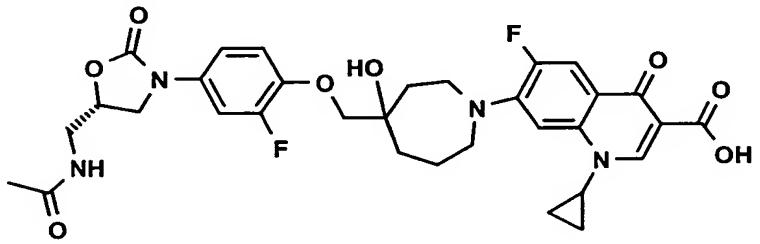
In analogy to example 76 with 48mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 367.38, 0.13mmol), 53mg of 1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (MW: 405.15, 0.13mmol) and 33mg of ethyl diisopropylamine (MW: 129.25, 0.26mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 41mg, 50 %. MS: 625.8 $(M+H)^+$, 623.8 $(M+H)^-$, Method ESI^+, ESI^-.

Example 86: 9-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



In analogy to example 81 with 110mg of 9-10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxilic acid (MW: 281.22, 0.39mmol), 143mg of N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.39mmol), and 100mg of ethyl diisopropylamine (MW: 129.25, 0.78mmol) in 2ml of N-methyl-pyrrolidin-2-one. Yield: 103mg, 42 %.MS: 629.8 $(M+H)^+$, Method ESI^+.

Example 87: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



Step 1: 4-Methylene-azepane-1-carboxylic acid tert-butyl ester:

A solution of 1g methyltriphenylphosphoniumbromide (MW: 357.22, 2.79mmol) in 20ml of tetrahydrofurane was treated at -78°C with 1.22ml of a 2.3 M n-butyl lithium solution in N-hexane (2.8mmol). The reaction mixture was stirred at -78°C for ten minutes, then at 0°C for one hour. The yellow suspension was cooled to -78°C and treated with a solution of 595mg 4-oxo-azepane-1-carboxylic acid tert-

butyl ester (WO 2000044376) (MW: 213.279, 2.78mmol) in 10ml tetrahydrofurane. The reaction mixture was stirred at room temperature for one and half hour. The reaction mixture was quenched with 30ml of a saturated aqueous solution of ammonium chloride, diluted with 30ml of ethyl acetate. The organic layer was successively washed with 30ml water and 30ml brine, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure and the residue purified by chromatography over silica. (cyclohexane:ethyl acetate 1:1). Yield: 487mg, 83%. NMR ($CDCl_3$): 1.35 ppm (s, 9 H, tert-but.); 1.6 ppm (m, 2H, $-CH_2-$), 2.14 ppm (m, 2H), 2.33 ppm (m, 2H); 3.29 ppm (m, 4H, $N-CH_2$); 4.67 ppm (m, 2H, vinyl-CH_2).

Step 2: 1-Oxa-6-aza-spiro[2.6]nonane-6-carboxylic acid tert-butyl ester:
In analogy to example 82 step 1 with 4-methylene-azepane-1-carboxylic acid tert-butyl ester (MW:211.307, 1.73mmol), 1.16g sodium bicarbonate (MW: 84.01 13.8mmol) and 1.36g of 80% m-chloroperbenzoic acid (MW172.57, 6.05mmol) in 5ml of dichloromethane. Yield: 250mg, 63 %. MS: 228.8 $(M+H)^+$, 127.8 $(M-(CH_3)_3COCO)$ method ESI^+.

Step 3: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepane-1-carboxylic acid tert-butyl ester:
In analogy to example 72 step 5 with 247mg of 1-oxa-6-aza-spiro[2.6]nonane-6-carboxylic acid tert-butyl ester. (MW: 227.31 1.08mmol), 296mg N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 80mmol) and 228mg potassium carbonate (MW: 138.20, 1.65mmol) in 150ml dimethylformamide. Yield:

334mg, 62 %. MS: 496.8 $(M+H)^+$, 440.8 $(M-C(CH_3)_3+H)^+$, Method ESI^+.

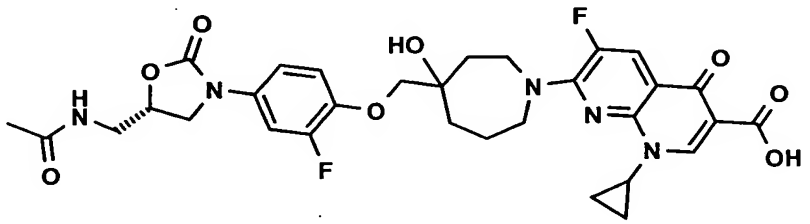
Step 4: N-{(5S)-3-[3-Fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide:

A solution of 334mg 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepane-1-carboxylic acid tert-butyl ester (MW:495.55, 0.674mmol) in 3ml of a 1.25 M anhydrous hydrogen chloride solution in methanol was stired at 35°C for four hours. The solvent was evaporated under reduced pressure. The residue was dissolved in 4ml water and the water layer neutralized to pH 7 with a saturated sodium bicarbonate solution. The water was evaporated and the residue dissolved in 30ml of a 9/1 dichloromethane/methanol mixture. The unsoluble salt were filtered and the filtrate evaporated to dryness to afford off white solid. Yield 266mg, quant. MS: 395.8 $(M+H)^+$, 440.6 $(M+HCOO^-)$, Method ESI^+, ESI^-.

Step 5: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

In analogy to example 76 with 150mg N-{(5S)-3-[3-fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 395.43) and 98mg of ethyl diisopropylamine (MW: 129.25, 0.758mmol), 163mg (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.397mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 70mg, 28.8 %. MS: 641.7 $(M+H)^+$, method ESI^+.

Example 88: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

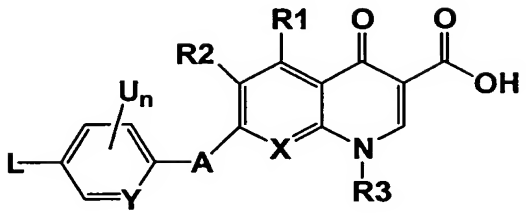


In analogy to example 72 step7 with 98mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW: 282.66, 0.348mmol), 138mg N-{(5S)-3-[3-fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 395.43, 0.348mmol), 140mg triethylamine (MW: 101.19, 1.39mmol) and 113mg trimethylchlorsilan (MW: 108.64, 1.04mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 150mg, 77 %. MS: 642.7 $(M+H)^+$, 640.7 $(M+H)^-$, Method ESI^+, ESI^-.

The compounds that were tested against several strains of *B. anthracis* showed MIC´s below 0.03µg/ml.

Claims

1. Use of a compound of Formula (I):

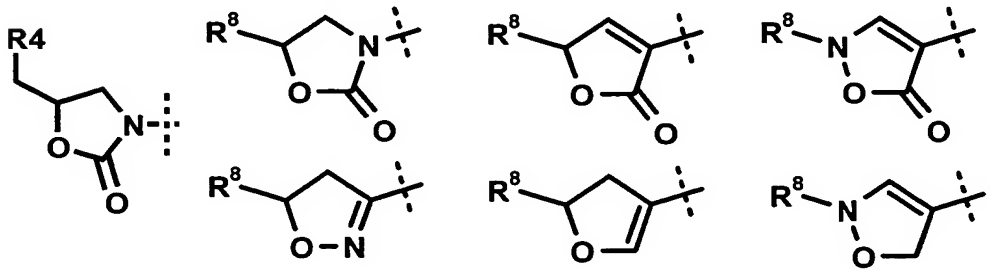


(I)

wherein

A is a bond, a NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, -CO-O-, -NH-CO-O-, -O-Z-heterocycloalkylen, an alkylen group, an alkenylen group, an alkinylen group, a heteroalkylen group, an arylen group, a heteroarylen group, a cycloalkylen group, a heterocycloalkylen group, an alkylarylen group or a heteroarylalkylen group or a combination of two or more of these atoms or groups;

L is selected from the following groups:



X is CR5 or N;

Y is CR6 or N;

U is F or Cl;

Z is a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group or a C_{1-4} heteroalkylene group, all of which may be substituted by one or more hydroxy or amino groups;

n is 0, 1, 2 or 3;

R1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

R2 is H, F or Cl;

R3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group; all of which may be substituted with one, two or more halogen atoms like F or Cl;

R4 is a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group;

R5 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R3 and R5 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a cycloalkylen or heterocyclo-alkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl;

R6 is H, F, Cl or OMe;

R8 is a C_{1-6} heteroalkyl or a heteroarylalkyl group;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof for the treatment of anthrax.

2. Use of a compound according to Claim 1, wherein R1 is H.

3. Use of a compound according to Claim 1 or 2, wherein R2 is F or H.

4. Use of a compound according to any one of the preceding claims, wherein R3 is an ethyl, a 2-propyl, a C_3-C_6 cycloalkyl, a phenyl or a pyridyl group, all of which may be substituted by one, two or more fluorine atoms or amino groups.

5. Use of a compound according to any one of the preceding claims, wherein R3 is a cyclopropyl group.

6. Use of a compound according to any one of the preceding claims, wherein R3 and R5 together form a group of the formula -O-CH_2-N(Me)- or -O-CH_2-CH(Me)-.

7. Use of a compound according to any one of the preceding claims, wherein R4 is an acetylamino group.

8. Use of a compound according to any one of the preceding claims, wherein the absolute configuration at C-5 of the oxazolidinone ring is (S) according to the Cahn-Ingold-Prelog nomenclature system.

9. Use of a compound according to any one of the preceding claims, wherein X is N or CH.

10. Use of a compound according to any one of the preceding claims, wherein Y is CF or CH.

11. Use of a compound according to any one of the preceding claims, wherein n is 0.

12. Use of a compound according to any one of claims 1-11, wherein A is a group of the formula

$$-B_{0-1}-\left[D-E_{0-1}\right]_m-G_{0-1}-K_{0-1}-$$

wherein

the group B is an alkylene, which may be substituted by one, two or more fluorine atoms, an O, S, SO, SO_2, SO_2NH group, or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group;

the groups D independently of each other are optionally anellated heterocycloalkylen groups with 1, 2, 3 or 4 nitrogen atoms, which heterocycloalkylen groups may each be substituted by one, two or more fluorine atoms and/or which each may be substituted at one, two, three or four nitrogen atoms by an alkyl or an acyl group;

the groups E independently of each other are an alkylene, which may be substituted by one, two or more fluorine atoms, an O, S, SO, SO_2, SO_2NH group, or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group;

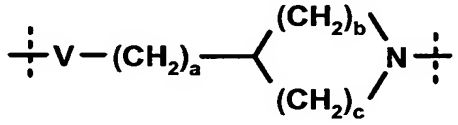
the groups G independently of each other are optionally anellated heterocycloalkylen groups with 1, 2, 3 or 4 nitrogen atoms, which heterocycloalkylen groups may each be substituted by one, two or more fluorine atoms and/or which each may be substituted at one, two, three or four nitrogen atoms by an alkyl or an acyl group;

the group K is an alkylene, which may be substituted by one, two or more fluorine atoms, an O, S, SO, SO_2, SO_2NH group, or a heteroalkylen group, which may be substituted by one, two or more fluorine atoms and/or at the optionally present nitrogen atoms by an alkyl or an acyl group; and m = 1,2,3 or 4.

13. Use of a compound according to any one of Claims 1-11, wherein A is a group of the formula -V-W-,

wherein V is a direct bond or a group of the formula NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, $-CH_2-$, -CO-O-, $-(CH_2)_{1-3}-O-$, -CH=CH-C(O)-, or -NH-CO-O- and W is a heterocycloalkyl group with 4 to 7 ring atoms or a alkylheterocycloalkyl group with 4 to 7 ring atoms and 1 to 4 carbon atoms in the alkyl chain; all these groups may be substituted by 1, 2, 3 or 4 fluorine atoms, methyl or methoxy groups.

14. Use of a compound according to any one of Claims 1-11, wherein A is a group of the formula



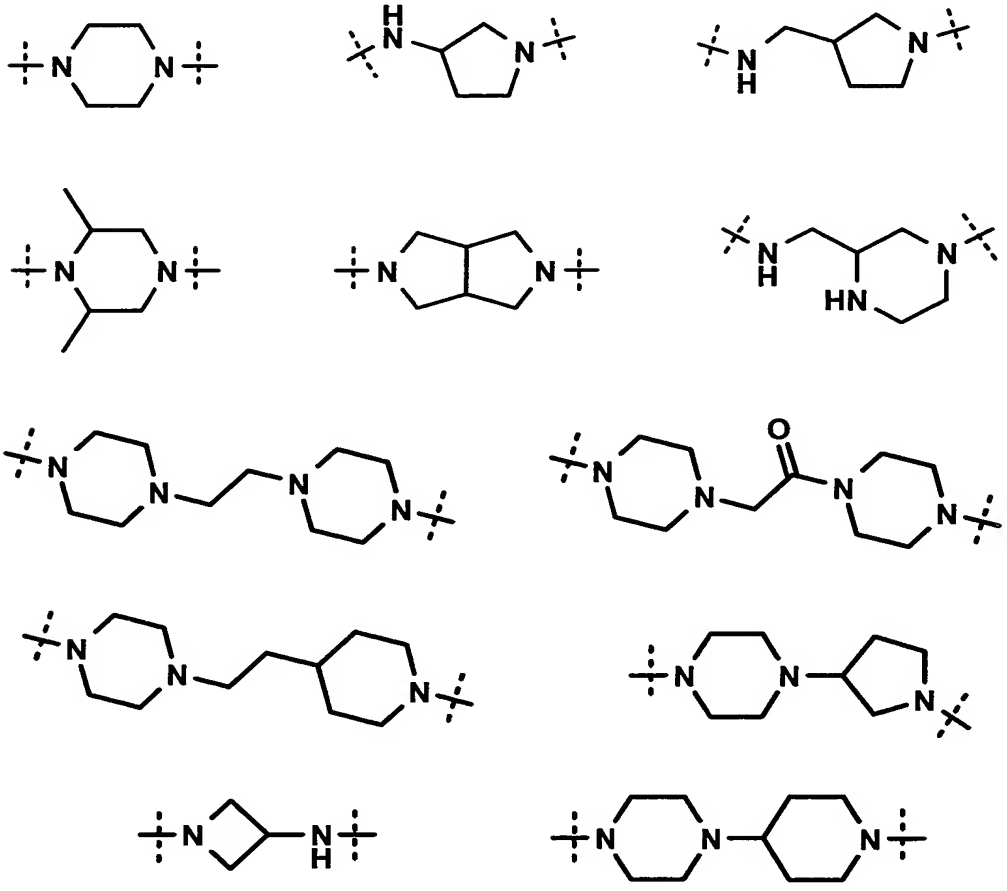
wherein

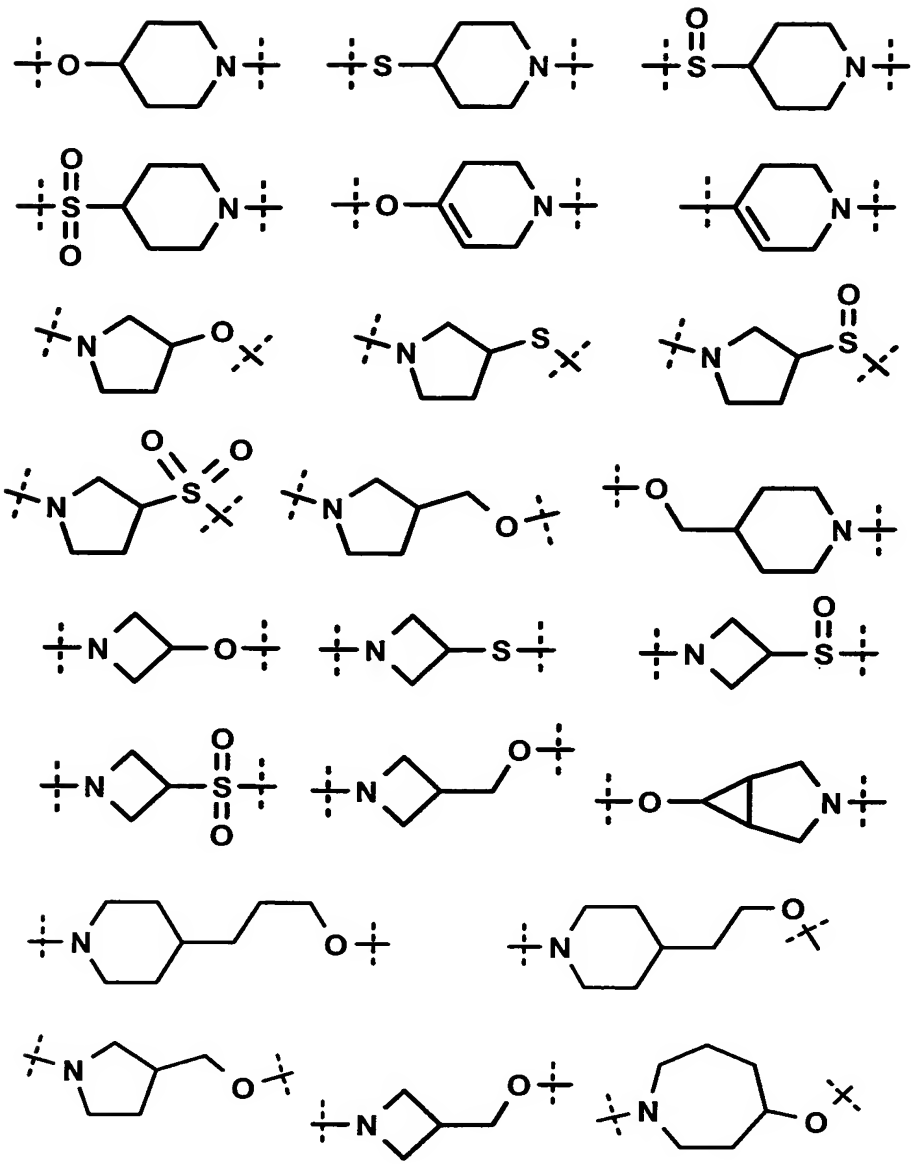
V is a group of the formula NH, O, S, SO, SO_2, SO_2NH, PO_4, -NH-CO-NH-, -CO-NH-, -CO-, $-CH_2-$, -CO-O-, $-(CH_2)_{1-3}-O-$, -CH=CH-C(O)-, or -NH-CO-O-; a is 0, 1, 2, 3 or 4; b is 0, 1, 2, 3 or 4; c is 0, 1, 2, 3 or 4 and 1, 2, 3 or 4 hydrogen atoms may be substituted by F, a methyl- or a methoxy group.

15. Use of a compound according to Claims 13 or 14, wherein V is NH, O, S, SO or SO_2.

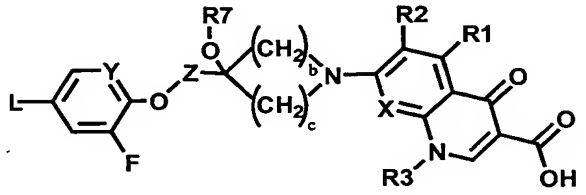
16. Use of a compound according to Claims 13 or 14, wherein V is O or NH; a is 0 or 1; b is 1 or 2 and c is 1 or 2.

17. Use of a compound according to any one of Claims 1-11, wherein A is selected from the following groups which may be substituted by one, two or more fluorine atoms or by an alkyl group which may be substituted by one or more fluorine atoms, and wherein the amino groups may be substituted by an alkyl or an acyl group:





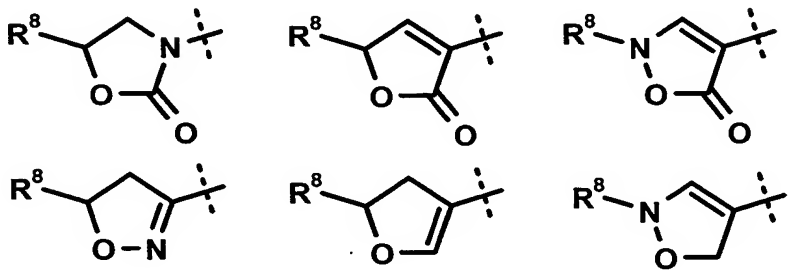
18. Use of a compound according to any one of claims 1-6 and 8-10, wherein the compound is represented by Formula (II):



(II)

wherein

L is selected from following groups:



b is 1, 2 or 3;

c is 1, 2 or 3;

R7 is hydrogen, a group of formula $PO_3R^9_2$ or SO_3R^{10} or a heteroalkyl group carrying at least one OH, NH_2, SO_3R^{10}, $PO_3R^9_2$ or COOH group, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl;

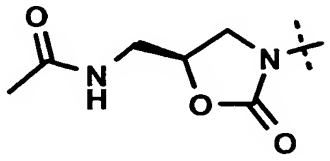
X, Y, Z, R1, R2, R3, R5, R6, R8, and the possible linkage between R3 and R5 are as defined above;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof for the treatment of anthrax.

19. Use of compounds according to Claim 18, wherein R7 is hydrogen or a group of the formula SO_3H, PO_3H_2, $PO_3(CH_2C_6H_5)_2$, CH_2OPO_3H or $COCH_2CH_2COOH$, or together with the oxygen to which it is bound forms an ester of a naturally occurring amino acid or a derivative thereof.

20. Use of compounds according to Claims 18 or 19, wherein R8 is a group of the formula -$CH_2NHCOCH=CHAryl$, - $CH_2OHeteroaryl$, -CH_2NHSO_2Me, -$CH_2NHCOOMe$, -CH_2NHCS_2Me, -$CH_2NHCSNH_2$, -$CH_2NHCSOMe$ or -$CH_2NHCOMe$.

21. Use of compounds according to any one of Claims 18-20, wherein L is a group of the following formula:



22. Use of compounds according to any one of Claims 18-21, wherein R5 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms.

23. Use of compounds according to any one of Claims 18-22, wherein Z is CH_2 or CH_2CH_2.

24. Use of a pharmaceutical composition containing a compound according to any one of the preceding claims and optionally carriers and/or adjuvants and/or diluents for the treatment of anthrax.

25. Use of pro-drugs, which contain a compound according to any one of the preceding claims and at least one pharmacologically acceptable protective group for the treatment of anthrax.

26. Use of a compound, a pharmaceutical composition or a pro-drug according to any one of the preceding claims for the manufacture of medicaments for the treatment of anthrax.

27. Use of a compound, a pharmaceutical composition or a pro-drug according to any one of the preceding claims for the treatment of infections.

Abstract

The present invention relates to the use of compounds, in which the pharmacophores of quinolone and oxazolidinone are chemically linked together through a linker that is stable under physiological conditions, for the treatment of anthrax and other infections.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003650

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4709 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HUBSCHWERLEN C; SPECKLIN J-L; SIGWALT C;ET AL: "Design, Synthesis and Biological Evaulation of Oxazolidinone-Quinolone Hybrids" BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 11, 15 May 2003 (2003-05-15), pages 2313-2319, XP002283439 cited in the application abstract; table 2	27
X	WO 02/059116 A (BARBACHYN MICHAEL R ; GORDEEV MIKHAIL F (US); UPJOHN CO (US); GAGE JAM) 1 August 2002 (2002-08-01)	27
Y	page 1, lines 11-18; example 1	1-26
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2004	18/06/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/002560 A (VITA INVEST SA ; DEL CASTILLO JUAN CARLOS (ES); HIDALGO RODRIGUEZ JOSE) 9 January 2003 (2003-01-09)	27
Y	page 2, lines 13-16; claim 8; examples 1,7	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/003650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02059116 A	01-08-2002	CA 2424402 A1	01-08-2002
		EP 1349853 A2	08-10-2003
		WO 02059116 A2	01-08-2002
		US 2003013737 A1	16-01-2003
WO 03002560 A	09-01-2003	ES 2186550 A1	01-05-2003
		CA 2450982 A1	09-01-2003
		EE 200400004 A	16-02-2004
		EP 1401834 A1	31-03-2004
		HR 20031063 A2	30-04-2004
		WO 03002560 A1	09-01-2003